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SCIENTIFIC PAPERS

DIABETES

a panel discussion touching on such considerations as prediabetes, prevention of diabetic complications, oral therapy, and management of unstable diabetes

Moderator
Henry T. Ricketts, M.D.[1]
Participants
T. S. Danowski, M.D.[2]
Francis D. W. Lukens, M.D.[3]

DR. RICKETTS: Prediabetes seems like a good starting point for this discussion. I'd like to ask Dr. Lukens to tell us a little about this subject. He attended a recent conference in Kalamazoo, sponsored by the Upjohn Company, devoted to this subject; and I am sure he has some ideas that we'd like to hear.

DR. LUKENS: A conference on prediabetes with no formal papers and limited in number was a thought-provoking experience. I have no intention of putting you through two days' worth of technicalities, but it occurred to me that we could say something about it. If diabetes is the condition of hyperglycemia and glycosuria, then prediabetes is a condition that does not have hyperglycemia and glycosuria, but it is the condition of a person who will develop diabetes eventually.

How do we study something we cannot see? This is a problem; perhaps it is best expressed

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in a definition of prediabetes that was developed at the Upjohn conference. Prediabetes is the state or condition of those persons who will eventually develop diabetes. The existence of prediabetes is established by the fact that diabetes develops significantly more often in certain types of individuals than in the general population. Such persons include the relatives of diabetics; individuals with abnormal carbohydrate metabolism during pregnancy, infection, or a positive cortisone-glucose tolerance test; mothers of large babies; and the obese. Follow-up until the appearance of diabetes or the establishment of better predictability of diabetes moves many of these people into the category of frank diabetes.

The biochemical and other abnormalties of the prediabetic state remain unknown. Now, you can see that there are just enough straws in the wind so that the word prediabetes is not entirely spurious. Prediabetes is like the proverbial invisible part of the iceberg under water. There's a good deal of it there, but it will take some doing to see all of it.

DR. RICKETTS: Have you any ideas, Dr. Danowski, about the class of people in whom you would look for prediabetes? Can you elaborate any further on that?

DR. DANOWSKI: You certainly might look for prediabetes among the obese, although it's well to point out that probably less than 5 per cent of the obese population does develop diabetes. You would look, too, among women who have a history of repeated miscarriages or perinatal deaths or who have given birth to large babies. You would look for diabetes in those who have, perhaps, undue glycosuria or real glucosuria during pregnancy.

DR. RICKETTS: Dr. Danowski, excuse me, but I didn't say look for diabetes; I said look for prediabetes. Where would you look for these people and how would you do it?

DR. DANOWSKI: Well, the moment you find it, it's no longer prediabetes; it's diabetes.

DR. RICKETTS: Well, now, is this really true? Do you agree with that, Dr. Lukens? Can you find what we would accept as prediabetes in the absence of classical symptoms, and how do you do it?

DR. LUKENS: Well, whatever I say will be arbitrary, and you won't like it.

DR. RICKETTS: I may not, but try anyway.

DR. LUKENS: Let's try this one. If you can find an abnormal cortisone-glucose tolerance and say that this is diabetes diagnosed at a somewhat earlier stage than was possible five years ago, as Dr. Danowski said, that moves it into the category of diabetes, but does so ahead of time. On the other hand, if you have the mother of a large baby who has a normal cortisone-glucose tolerance test but who is more likely to develop diabetes twenty years later, you have, perhaps, found a prediabetic who is not yet diabetic. This may sound like a mere question of semantics, but it doesn't hurt to think about these things if we are going to have some forethought about a lifelong genetic disease and if we are going to think more in terms of preventive measures.

DR. RICKETTS: All right. The cortisone-glucose tolerance test has been referred to. I wonder how many of the audience are familiar with this procedure. Briefly, it is the giving of cortisone before a glucose tolerance test. In this situation, the number of people responding with an abnormal glucose tolerance curve is far higher among those with family histories of diabetes than it is among the general population.

It goes a little deeper than this, but perhaps this explanation is sufficient. Now, Dr. Danowski, suppose you did this cortisone-glucose tolerance test on the child of a diabetic family, said child not being frankly diabetic at the time, and it turned out to be positive; it turned out to be a diabetic type of curve under the influence of cortisone. What would you do with that child?

DR. DANOWSKI: This is a difficult question to answer—

DR. RICKETTS: It's intended to be.

DR. DANOWSKI: I think it becomes a philosophic problem. I would be inclined to try to make the abnormal glucose tolerance tests under the influence of cortisone disappear; in other words, I would attempt to reverse this state. I don't know whether this could be accomplished. We have some evidence that it can be done in adults. I would use the traditional measures employed in the therapy of diabetes; by that I mean dietary restriction, largely. Then, on an experimental basis, I would administer oral hypoglycemic agents. I emphasize that this is on an experimental basis.

I think that the difficult problem is that of

conveying to the family just what you are doing, because, on the one hand, you will be telling them that the child does not have diabetes. Then when they talk to the neighbor, they discover that you're treating the child as a diabetic. This is a rather difficult horse to straddle.

DR. LUKENS: May I comment on that? It doesn't matter what you do for the child provided you are careful to watch it. One must develop the index of predictability under this situation, and you may do that with or without any form of treatment. But don't let the child go and don't be indifferent.

DR. RICKETTS: Well said. You wouldn't be afraid, would you, that by giving the child Orinase®, you might exhaust his pancreas?

DR. DANOWSKI: Yes, I would be afraid. On the other hand, I might justify it in these terms: that, actually, the demonstration of an abnormal curve moves that patient into the diabetic category; therefore, I would have no qualms about treating such a patient. The end products might well include so-called secondary failure.

DR. RICKETTS: I take it that you wouldn't be disposed to give this child insulin. That would be going too far. Is it true, then, that the next best thing would be the oral drugs? Is that your philosophy?

DR. DANOWSKI: This would be my general feeling at this time, although I would not have a very strong argument against insulin, certainly. If we did not have oral hypoglycemic agents at this time, I would be greatly tempted to give insulin in line with Dr. Lukens' original observations indicating a possibility of regeneration of islets that are becoming exhausted.

DR. RICKETTS: I think your point of view is entirely reasonable. We agree that we ought to do something about people of this kind, but we must be careful not to do so much, say, prescribing insulin for the *absence* of glycosuria, that they will leave us and go to another physician. Among the things that we must do, I'm sure you agree, are preventing obesity and possibly recommending a low carbohydrate diet.

Speaking of exhausting the beta cells, I expect we've about exhausted the subject of prediabetes. Now let us pass on to another topic of great interest in connection with diabetes; namely, the prevention of vascular complications.

This is a perennial puzzle which nobody has solved yet. Our clues as to the pathogenesis of vascular disease in diabetes are still meager indeed, and I suppose it is fair to say that no one has arrived at an answer that meets all the circumstances. In the first place, we don't know what it is about the biochemical abnormalties of diabetes that might predispose to atherosclerosis, retinopathy, and renal disease. We don't know whether it is hyperglycemia or hyperlipemia or some other unknown biochemical concomitant of diabetes that initiates the vascular degeneration so characteristic of this disorder. We might as well admit outright that we don't know what it is.

Now, if we move to the next question, whether it is the control of diabetes that influences the appearance of these lesions, we again have to hedge. We really are not sure.

We must remember certain facts. One is that we commonly see diabetic patients whose disease is so mild that it has to be diagnosed by a glucose tolerance test, but who, nevertheless, present at their first examination a well-defined retinopathy. These patients without glycosuria demonstrate that severity of diabetes is not necessarily related to the appearance of vascular lesions. Severity of diabetes may be related to the severity of lesions, but definitely not to their appearance alone. We must consider whether or not the tendency toward these vascular troubles is inherited along with the tendency to diabetes itself; however, we don't know enough about our human genetics to give a clear answer.

At the other end of the scale, we are aware of a number of patients with no family history of diabetes who have been subjected to total pancreatectomy for one reason or another—chronic relapsing pancreatitis with calculi, some cases of carcinoma—who have been followed for five, six, seven, or eight years after the onset of this induced diabetes, and who at the end of that time have been found to have well-documented diabetic retinopathy. This condition is not spontaneous diabetes; the disease has been induced. If these individuals are indeed without a hereditary taint, then we have to say that either diabetes in and of itself or the presence of something connected with diabetes is capable of producing such lesions.

These suppositions are the two ends of the

scale; where the truth lies, I'm sure we don't know at this time. I would be glad to hear amendments, disputations, agreements, or whatever from my colleagues. Dr. Danowski?

DR. DANOWSKI: There are a number of subjects that one should not discuss, either in public or privately; for example, it's generally unwise to discuss a man's wife with him, and secondly, it's probably unwise to discuss his religion. In some circles, it's extremely unwise to discuss the question of how to treat diabetes and whether such treatment prevents vascular disease. The reason is that all of these subjects represent emotional involvement.

Statistics are available to show clearly a low incidence of vascular disease in some clinics as compared to other clinics. Now, this might reflect either superior therapy or a process of selection; indeed, I am sure that such selection goes on. For example, if I am not pleased with the behavior of a patient, I probably manifest it in some way. Thus, I communicate to the patient, the patient is unhappy, and he soon leaves me. If I keep this up for 40 years, I'll have a group of patients all of whom do exactly what I say and look the way I want them to look; then I can go on and speak *ex cathedra*. Those of us who work in clinics, however, cannot accumulate such a group of patients; and I think that whenever you see a set of statistics from a competent group of people, you must consider how their statistics were assembled.

DR. RICKETTS: Dr. Lukens, any ideas, disagreements?

DR. LUKENS: What Dr. Ricketts and Dr. Danowski have pointed out, I think, is that there are two working hypotheses. The inheritance of a vascular defect is a fairly popular working hypothesis. If you can carry on investigations with this in mind and add something to it, that's fine. I happen to take the other working hypothesis because I think it enables me to do more things I'd like to do.

I am worried by a phrase that has slipped into the conversation; that is, "control of diabetes." I've spent a good many years wondering what it means. When we talk about control, people automatically think of freedom from glycosuria and normal blood sugar level, normal body weight, and normal growth of the child.

What defect exists in the mild diabetic who hasn't yet been diagnosed, and what defect exists in the diabetic who takes full doses of insulin and is free from glycosuria, but is still developing these things? Since we haven't yet measured this defect and the biochemist is far from telling us about it, this seems to me to be a highly fertile field of investigation. For this reason, I assume, purely as a working hypothesis, that all of this is a complication of the lack of insulin. This hypothesis compels me to wonder more and more what are those effects of a lack of insulin which still are unseen or not understood when one measures blood sugar.

DR. RICKETTS: One might think that the way to work this problem out might be in using experimental animals, made insulin-deficient, as these few patients I mentioned were made insulin-deficient, by pancreatectomy or various other means, to study what happens to the vascular tree under such circumstances. This has been done in a number of species of animals with quite disparate results, as a matter of fact.

To say that no one has succeeded in duplicating the human lesion, although true, is perhaps unfair. Can you expect a rat, if he develops vascular trouble, to develop the same kind that you and I would if we had diabetes? This is asking quite a lot of the rat. In dogs, efforts have been made to produce experimental diabetes and to follow or demonstrate lesions of this kind. In my own experience of some eight years with experimental diabetes in dogs, no typical diabetic vascular disease was found in any animal. So, although insulin deficiency may be a factor, it has not been possible to demonstrate it by experimental means, except in man.

DR. LUKENS: And the rat.

DR. RICKETTS: Well, I would say perhaps. You're talking about the experimental lesions of the renal glomeruli. They may be the same as KW lesions in man. If they are, this is fine, if they're not, it wouldn't surprise me, even though they may be due to insulin deficiency.

DR. LUKENS: They're still diabetic.

DR. RICKETTS: Yes, it's perfectly true, they are.

Dr. Danowski has raised the question of the difference between large vessel disease and small vessel disease in diabetes. Would you like to elaborate on that?

DR. DANOWSKI: While we are grossly ignorant about blood vessel diseases, perhaps our ignorance is a bit less pronounced in the case of the large blood vessels. The diabetic is more prone to myocardial infarction and to peripheral arterial obstruction. Such large blood vessel changes also occur in the population as a whole, and a body of evidence is accumulating which indicates that dietary factors and a host of other variables affect the frequency of such large blood vessel disease. These changes in the large blood vessels are to be differentiated sharply from the retinal lesions and the specific or fairly specific kidney lesions and possibly the lesions of the blood vessels of the nerves of the diabetic. In the realm of these small blood vessel changes in the diabetic, our ignorance is profound indeed.

DR. RICKETTS: I quite agree, and I'm sure everybody would, with these statements. Now, if it's important to render the patient as normal as we can, let me ask Dr. Danowski, who has had the most experience with unstable diabetics, in whom this goal is so difficult to achieve, what methods of treatment he uses to control his young patients.

DR. DANOWSKI: The method of compromise. Actually, I think that I should begin with the statement that I try to keep a diabetic child as normally glycemic and as aglycosuric as possible without shocking him and, without imposing stringent conditions that make life hardly worthwhile for a youngster. This goal may be achieved in a certain number of youngsters. Some children can be maintained on dietary restriction alone; however, these are most unusual. Most of the time, as you know, insulin is required because of energy and growth needs.

Once they have set their goal, many physicians are unwilling to modify it for the particular child with whom they are dealing. A tranquil attitude in approaching the problem and self-confidence are crucial, I think. Too often the physician feels that he doesn't have all the known facts about diabetes at his command or that he doesn't know everything about the youngster; that if he did, perhaps he could achieve this goal. Actually, the goal may be unattainable, and a philosophic attitude is necessary. Such a response tends to minimize frantic behavior on the part of the doctor and frantic behavior on the part of the family. It removes a strong emotional component from the atmosphere; and one may achieve a measure of acceptable control in this circuitous fashion. Otherwise, if one insists that every diabetic child be put into the same pattern that I described initially, he is doomed to failure and the patient is doomed to inadequate care.

DR. RICKETTS: What applies to the diabetic child applies in large measure to the unstable adult diabetic also?

DR. DANOWSKI: I would think so. I like to divide the unstable adult diabetics into those who are unstable because of themselves and those who are unstable because of their doctors. The second category is perhaps more readily amenable to therapy. Some of these are instances of unrecognized hyperinsulinism, patients who come in with insulin dosages of 100 units or more, labeled brittle diabetics. You put them in the hospital, reduce the dose of insulin ultimately to 30 units, and the patient goes out no longer brittle. This is iatragenic hyperinsulinism; i.e. brittle diabetes created by the doctor, and is to be differentiated from the real brittle diabetes which I suppose, Dr. Ricketts, is the disease that you, Dr. Lukens and I can't cure.

DR. RICKETTS: In the handling of adult brittle diabetes, I have been impressed over the past ten years with what can be done by means of multiple injections of regular insulin rather than by the use of any single long-acting preparation, be it NPH or Lente or any combination of insulins given as a single dose in the morning.

The probable reason for the instability of many people with diabetes would seem to be that they're not able to produce enough insulin of their own. Now, this is somewhat conjectural, admittedly.

Dr. Wrenshal and his colleagues in Toronto analyzed the insulin content of the pancreas in people of various age groups. Diabetics dying between 20 and 30 years of age, 40-60, and 60-80 have about half the insulin content of the nondiabetics of a comparable age group.

On the other hand, in diabetic children and young people under twenty, one finds almost no insulin in the pancreas compared with the normal or nondiabetic of comparable age. This depletion of insulin content in the pancreas, while not absolutely the cause of instability of diabetes, probably has a good deal to do with it, for such patients totally lack the homeostatic mechanism that even the moderately impaired pancreas has to put out

insulin when it's needed and to pull it back when the need has passed.

In extremely unstable diabetics, we can come a little closer, I think, to meeting these exigencies by using regular insulin alone, insulin with a sharp, decisive, and uniformly timed activity, and dividing it into several doses at various times of the day. One patient was first maintained on Lente insulin alone as a single daily injection with severe glycosuria and blood sugars all over the place. When multiple doses of regular insulin were begun —before breakfast, before supper, and at 2:00 A.M.—the remarkable stability that ensued seems to be perfectly evident.

In a similar case, not quite as dramatic, protamine zinc and crystalline insulin given together produced erratic behavior of the four times a day blood sugars. When regular insulin alone was given and the proper dose finally achieved, stability was considerably greater and glycosuria considerably less.

Another patient had tremendous fluctuation of the blood sugar on Lente insulin with a little regular, glycosuria reaching sixty grams a day. Multiple doses of regular insulin alone worked much better. I shouldn't call it ideal, but quite a lot better, and glycosuria became considerably less.

This is all I have to say about this method. It's a little Spartan for children; it's kind of a hardship, and we don't use it often, but for the real tough ones I think it does hold possibilities.

DR. LUKENS: I couldn't agree with you more. But does this always work, I'd like to know?

DR. RICKETTS: No, it does not always work.

DR. LUKENS: I think that's the dilemma. But it works enough to keep a certain number of patients out of trouble.

DR. RICKETTS: Yes.

DR. LUKENS: As for being a hardship, every now and then you find an informed patient who comes and says, "Doctor, may I change my depot insulin to four doses of regular insulin a day. I feel better that way." For those people it is certainly no hardship.

DR. RICKETTS: Well, I think we should turn to the questions now, unless the panel has further spontaneous comments to make. The first question that I have says, "What is the technique of the cortisone-glucose tolerance test?" Dr. Danowski, have you used this, so that you know?

DR. DANOWSKI: Yes. We have used it, but we haven't used Dr. Conn's specific procedure, which, I believe, involves the administration of cortisone the evening before and then a subsidiary dosage before the test itself. We have been giving 200 milligrams 45 minutes before the tolerance test. Dr. Conn's criteria are sugars significantly above 120 at the two-hour point. A patient who on a cortisone tolerance test consistently shows sugars above this level is said to have an abnormal tolerance test. Conn has enough evidence to indicate that over a period of years some of these patients go on to develop manifest diabetes.

DR. RICKETTS: Dr. Lukens, is this your understanding of the cortisone-glucose tolerance?

DR. LUKENS: Yes. There are minor modifications, but that's it in essence.

DR. RICKETTS: Here's a question. "In the hypothetical case of the child of diabetic parents who has an abnormal cortisone-glucose tolerance test, would you continue to administer cortisone so that you can observe the results of your diabetic therapy? If not, what criteria do you have to judge the efficacy of your therapy in an asymptomatic individual?" Dr. Lukens, would you continue to give cortisone to—

DR. LUKENS: Well, no; as I understand it, this refers to one or two doses of cortisone given just before the tolerance test.

DR. RICKETTS: Yes, but I think the inquirer wants to know whether you know what you're doing unless you continue to stress the patient with cortisone. Is that right?

DR. LUKENS: Oh, you mean should we repeat the cortisone dose tolerance test at six-month intervals?

DR. RICKETTS: No, should you continue to administer cortisone? I think he must mean daily.

DR. LUKENS: No, I certainly wouldn't do that, if that's what's meant.

DR. RICKETTS: "If regulation as judged by a blood sugar is good, is there any harm in a high fat diet for the patient's arteries?"

DR. DANOWSKI: Well, I wouldn't think of it that way. As a matter of fact, one of the problems that's well worth investigating is whether the diabetics on the ADA diet are receiving too much fat. The diet of the diabetic contains 45 per cent of the calories in the form of fat, and investigators in the area of large blood vessel disease in non-

diabetics tell us that this is all wrong, that it should be down to 25 per cent or less.

Historically, of course, it's easy to understand how we got up to 45 per cent fat. Initially carbohydrate was restricted, and the patient could eat only a limited amount of protein. Since he needed calories, these were provided in fat. Now, with sufficient quantities of insulin available, there may not be need for it.

We have been exploring the possibility of 25 per cent, and indeed even 12½ per cent, fat diets. The 25 per cent diets are well tolerated by patients. A psychologic hazard is that it provides a much larger intake of carbohydrates than the patient and his family are accustomed to; yet this does not increase the glycosuria, nor does it raise the insulin requirement. I think it's well worth looking into further, because this would then mean that there would be available larger quantities of carbohydrate for reglycogenation of the liver, reglycogenation of muscles, and the reduction of ketone bodies. The last is highly desirable because it's the deglycogenated liver that produces ketone bodies in excess. I think, however, that the low fat-high carbohydrate diet is still an open question, but I would look at it from that viewpoint rather than the one that the question suggested.

DR. RICKETTS: Dr. Lukens, do you have a comment on this?

DR. LUKENS: Well, regardless of the actual amount of fat eaten, one will judge the effectiveness of the diet on the blood lipids. An actively exercising child can tolerate a lot of fat, in all likelihood. Your children are not hyperlipemic, are they?

DR. DANOWSKI: No.

DR. LUKENS: Whereas the adults certainly need the low fat diet, as Dr. Danowski says. By the way, Mr. Chairman, we may have been a little unjust with this first question. I've had time to look it over. There is a part of it which is very relevant: it says, "If not"—meaning if not by giving cortisone—"what criteria do you have to judge the efficacy of your therapy in an asymptomatic individual?"

It seems to me that a standard glucose tolerance test performed once or twice a year is probably the first means that would be used. I would not want to brush off a question as highly intelligent as that.

DR. DANOWSKI: That would be a good way to judge the inefficacy of therapy, because the ordinary tolerance test in such a patient is normal, and cortisone makes it abnormal. Now, if you repeat the ordinary tolerance test and after a year it is abnormal, then your regimen has been inefficient.

DR. LUKENS: That's right.

DR. RICKETTS: Good, we agree. Let's go on to another subject, more controversial. I have a lot of questions here, but of all the questions I've seen, this appeals to me as being the most thought-provoking and stimulating. I'm going to read it to you just as it stands: "Does the lowering of blood sugar with DBI® really do the diabetic patient any good?" I think this is a wonderful question. Who wants to tackle it?

DR. LUKENS: Mr. Questioner, we are far from knowing whether lowering the blood sugar by any stated method does the diabetic any good. Indeed, we'd better ask, what good? In experimental diabetes, I have lowered the blood sugar by phlorizin and done the islands a lot of good; but to say whether doing this with DBI® does the patient as a whole any good will require probably another fifty or a hundred years of biochemical research. Certainly ten or fifteen years of observation will be necessary to see how many patients so treated fail to develop vascular complications by comparison with a control group.

DR. RICKETTS: Dr. Danowski, would you agree with that?

DR. DANOWSKI: Yes, I think that this is fair. I think that the whole subject of sulfonylureas and of DBI® could be viewed in this fashion. The real hope is that these represent new checkers introduced into the game and conceivably the use of these agents will alter the outcome in terms of long-standing complications or concomitants.

DR. LUKENS: May I suggest a specific one? If you read the right textbook of opthalmology, you will find that some people think hyperglycemia is closely related to cataract. These drugs might well prevent cataract but not prevent any vascular complications. We must be prepared to see differentiation of this sort.

DR. RICKETTS: The popularity of these oral preparations is greater than they deserve, in my opinion, but the fact they are so popular at least entitles them to more discussion than we have given some of the other topics: so we'd like to

pursue this subject. Another questioner would like to know what the mechanism is of a hypoglycemic action with DBI®? Does anybody want to undertake this one?

DR. DANOWSKI: The sulfonylureas, that is to say tolbutamide and chlorpropamide, enhance the flagging ability of the pancreatic islands to put out more insulin. Possibly it may also have an effect, either directly or through insulin, in suppressing the output of sugar by the liver.

Now, in the case of DBI®, there is no good evidence that the output of insulin is enhanced or that the output of glucose by the liver is suppressed. There are, however, some suggestive data that one aspect of the breakdown of the glucose molecule is altered; as a matter of fact it is accelerated. This occurs in one phase of the glycolytic process; i.e. in the hexosemonophosphate shunt, which operates at a much faster rate. Some insulin is required for the operation of the process. Acceleration of the shunt throws into the metabolic pool end products. At this particular point the real arguments begin; i.e. whether acceleration of anaerobic glycolysis is bad. In fairness to the drug, I ought to point out that, although experience is still limited, it has so far been a relatively benign agent.

DR. RICKETTS: Would you agree with the commonly made statement that the principal action of DBI® is to promote the breakdown of glucose by tissue anoxia?

DR. DANOWSKI: This statement, I think, is a bit unfair—

DR. RICKETTS: Frightening, isn't it?

DR. DANOWSKI: Yes, it's bad, because actually all sugar is broken down by anaerobic glycolysis; and what is being done here accelerates this process.

DR. RICKETTS: Dr. Lukens, do you have any standard method of judging the people in whom these drugs are going to be effective?

DR. LUKENS: Well, I have a purely private method.

DR. RICKETTS: Would you share it with us?

DR. LUKENS: If they need but little more therapy than diet alone, the drugs may be effective. I have been impressed with the failure of most writers to think quantitatively about the sulfonylureas. If they act upon the islands, as Dr. Danowski says and as everyone agrees, how much insulin is liberated? You can practically duplicate the fall in blood sugar induced by tolbutamide by two to four units of intravenous insulin, which certainly is not a large dose. If the patient needs that small help, we're happy to give it to him in this way; but it certainly explains why these drugs are not adequate in infection or any complication.

Another question is how much they reduce the glucose output by the liver. Experimentally, I can cite you a figure in which, at one hour after tolbutamide, the output of glucose in a dog's liver is zero. That is not true in every ambulatory diabetic, as we all know; but we don't know how much of this does happen. We ought to keep asking the question, how much? Then I believe we'd have a more sober approach to the use of these drugs.

DR. RICKETTS: What I really meant to ask was, do you do any tests to find out whether a patient will respond to tolbutamide, for example, or do you just give it a whirl and see how he gets along?

DR. LUKENS: Yes, that's it.

DR. RICKETTS: The latter? This is what I do, too; I think it's the best way. Single dose response tests are apt to be deceptive rather than predictive, much as we would like to have such tests. Dr. Danowski, in the handling of your unstable diabetic children, do you find that the administration of DBI® or sulfonylurea in addition to insulin has any stabilizing effect on their fluctuations?

DR. DANOWSKI: I can't answer that; we have practically no patients on these agents. It's true that one can find maybe one out of seven prematurely onset diabetics who will respond to sulfonylurea.

DR. RICKETTS: I don't think I made myself clear. I don't mean giving children these drugs in place of insulin, I mean supplementary to insulin.

DR. DANOWSKI: No—

DR. RICKETTS: The claim has been made by a number of people that this stabilizes these wide fluctuations. Have you tried it in this connection?

DR. DANOWSKI: Yes, I've tried it on brittle diabetics and in children, but I cannot see that it does.

DR. RICKETTS: This is either sulfonylureas or DBI®?

DR. DANOWSKI: That's right.

DR. RICKETTS: I'm delighted to hear you say that. This has been my own experience. It's not wide, I must confess, but I haven't seen any such results. It's curious how these reports get started.

They appear in the literature with great enthusiasm and with some documentation—yes, you have an idea?

DR. DANOWSKI: It's easy to understand how these reports start. The patient who is given DBI® and insulin visits his doctor once a week instead of once a month, he receives four times the attention he formerly did, he follows his diet more closely, and he does everything else better; so he's more stable.

DR. RICKETTS: I don't agree with that. I believe he might be better controlled, but I don't believe he's more stable. I think the unstable diabetic remains so no matter how often he sees his doctor. Maybe his overall sugar levels are lower, but the instability continues. Do you agree with that?

DR. DANOWSKI: Yes, but it depends on which doctor he's going to.

DR. RICKETTS: This is getting awfully personal. I'm not sure we ought to go on.

DR. DANOWSKI: Well, present company, of course.

DR. RICKETTS: Very good. Somebody would like to know the dosage of Orinase® and its variations. Certainly not more than 1.5 grams per day, half a gram three times a day, ought to be the maximum that is used. The majority of people, if they respond at all, get along with two doses a day, namely, half a gram twice daily. It must be given twice daily for best effect because its duration is a little like that of ordinary insulin. It is largely dissipated within eight or ten hours and must be repeated if twenty-four hour control is to be maintained.

With chlorpropamide (Diabinese®), on the other hand, a single dose each morning is adequate to control a twenty-four hour period, if control is possible at all. DBI® is more like Orinase®; it must be given in divided doses. The initial trouble with chlorpropamide and its reported toxicity arose, in large part, because physicians tried to give it in the same dose as they had given Orinase®, which was far too much. More than a few cases of toxic hepatitis were reported following the use of large amounts of this drug. Now that physicians have learned to use it in proper dosage, such reports are rare. We are still disturbed somewhat by the hypoglycemic episodes that occur with chlorpropamide, even on the recommended dosage. I presume that this is because the material is excreted slowly, blood levels are maintained higher for a longer time, and a missed meal or a little extra exertion may produce hypoglycemia with this drug, whereas it rarely does so with tolbutamide.

Dr. Danowski, you're the child specialist here; have you used mixed NPH and PZI in children?

DR. DANOWSKI: The two together? No. The mixing of PZI and regular, yes, although very seldom nowadays; the mixing of NPH and regular we do practice frequently nowadays.

DR. RICKETTS: A last question; which is the best oral hypoglycemic agent? Dr. Lukens, what's your vote?

DR. LUKENS: The best oral hypoglycemic agent is the correct diet, which has received the least discussion this afternoon.



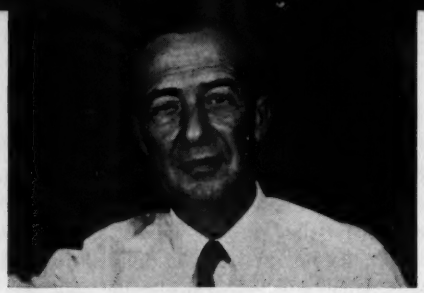
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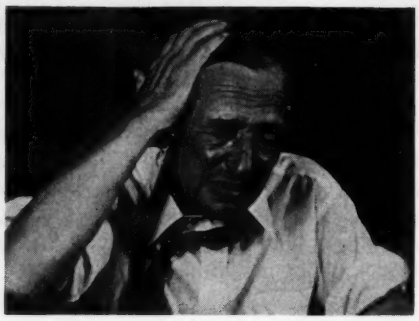


Fig. 1
Patient with histaminic cephalgia (case 5). *a*. Before an attack. *b*. During an induced attack of right histaminic cephalgia. *c*. Close-up of eyes before the onset of the attack, showing right Horner's syndrome. *d*. Close-up of eyes during the attack. (Photograph was retouched to show the tearing, but the untouched photographs also showed it clearly.) Pictures are from the first motion picture I ever made of a patient in an attack of histaminic cephalgia, and I believe it is the first in the history of medicine (photographed by L. A. Julin).

Bayard T. Horton, M.D.

HISTAMINIC CEPHALGIA

(HORTON'S HEADACHE OR SYNDROME)

Histaminic cephalgia is an unusual kind of headache with typical symptomatology that, once encountered, is never forgotten. The brevity and severity of the pain, its tendency to awaken the patient an hour or so after he has gone to sleep at night, and the accompanying localized vasomotor phenomena are the outstanding characteristics (figs. 1 and 2). It occurs chiefly among men and is a distinct clinical entity (1-17).





Historical Background

In 1940, I coined the term "histaminic cephalgia." The syndrome was first fully described with illustrative cases in an article published early in 1941 (2). I had presented this report at the meeting of the American Medical Association on June 12, 1940. Technicolor motion pictures were used for the first time to illustrate the full-blown clinical picture.

Clinical investigators agree that the clinical picture which I have chosen to call "histaminic cephalgia" exists, but some still think that it should be classified as migraine or a migraine equivalent. I was loath to break away from the concept that all periodic headaches are migraine, as evidenced

Presented April 22, 1960, at the Annual Meeting of the Medical and Chirurgical Faculty of Maryland.



Fig. 2

Appearance of a man during the course of an induced attack of left histaminic cephalgia, which developed 45 minutes after the subcutaneous injection of 0.4 milligram of histamine base. A histamine provocative test with 0.35 milligram of histamine base previously did not provoke an attack. The attack was typical, beginning as a tingling sensation in the left nostril. Beads of perspiration are evident above the left eye, with profuse lacrimation of the left eye and rhinorrhea from the left nostril. A distended vessel is visible in the left temporal area. At the height of the pain, which was confined to the left side of the head, punch biopsy of the skin from both temporal areas (pain area and control area) was made for study of mast cells. (Photograph was retouched to show the tearing clearly.)

by the fact that the title of our original preliminary report at the staff meeting of the Mayo Clinic, March 30, 1938, read: "Migraine: Treatment With Histamine." This paper was not published. After this address, some of my colleagues were frank enough to say, "You are not talking about migraine or a migraine equivalent; you must be talking about a new disease entity." As research continued, I became more and more convinced that this was a new disease entity, not migraine. So I discarded the original title and published the observations (12) on April 26, 1939, as a new syndrome of vascular headache.

In the twelve years before that publication, I had observed a few patients with erythromelalgia of the feet and had been impressed with their complaints of burning distress. Extreme degrees of vasodilation were associated. In my early studies of thirty patients with this new type of headache, I demonstrated, by means of electric thermocouples, an increase in surface temperature of the painful areas during both induced and spontaneous attacks in an environmental temperature of 78° F. and 40 per cent humidity when patients were in a basal state. Thinking of the head as a fifth extremity, therefore, I suggested the term "erythromelalgia of the head"—a burning type of pain roughly corresponding to the anatomic distribution of the branches of the external carotid artery, as descriptive of this new disease entity. This term proved to be too cumbersome for daily use, and it gave no clue to the basic disturbance.

The fact that attacks could be provoked by the subcutaneous administration of histamine and aborted with epinephrine, added to fact that histamine desensitization could be employed successfully in the treatment of the head pain, led me to believe that the condition was some disturbance in histamine metabolism in a localized area at the cell level; hence, the birth of the term "histaminic cephalgia," which I have continued to use.

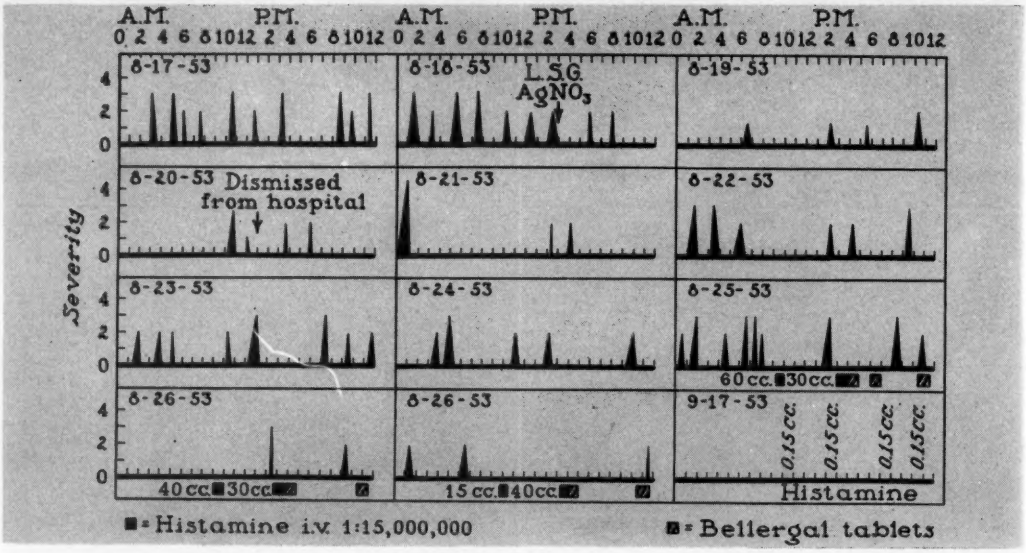


Fig. 3

Number and severity of attacks of left histaminic cephalgia. Patient was in a fourth series of attacks when admitted. This series had begun in December 1952 and had occurred both day and night at about the same frequency. On August 18, 1953, because cocainization of the left sphenopalatine ganglion area had given temporary relief earlier, silver nitrate ($AGNO_3$) was applied to the left sphenopalatine ganglion. The severity and frequency of attacks decreased, and the patient was dismissed from the hospital; however, the attacks continued to recur. Details regarding treatment are not included.

For twelve consecutive days, after August 26 (not depicted in the graph), he was given 1 milligram of PT-9 four times daily. Dosage was increased until he was taking 1 milligram at hourly intervals during the waking hours. The frequency and severity of attacks were greatly reduced. Upon discontinuance of PT-9, he had twelve attacks in the next forty hours, whereas he had had only five attacks in the previous eighty-four hours. Intravenous administration of histamine in a 1:15,000,000 solution, as illustrated in the graph, seemed to block attacks more promptly than any of the other procedures employed. At the time of dismissal he was taking 0.15 cubic centimeter of histamine subcutaneously four times daily, and had been entirely free from pain for seven consecutive days.

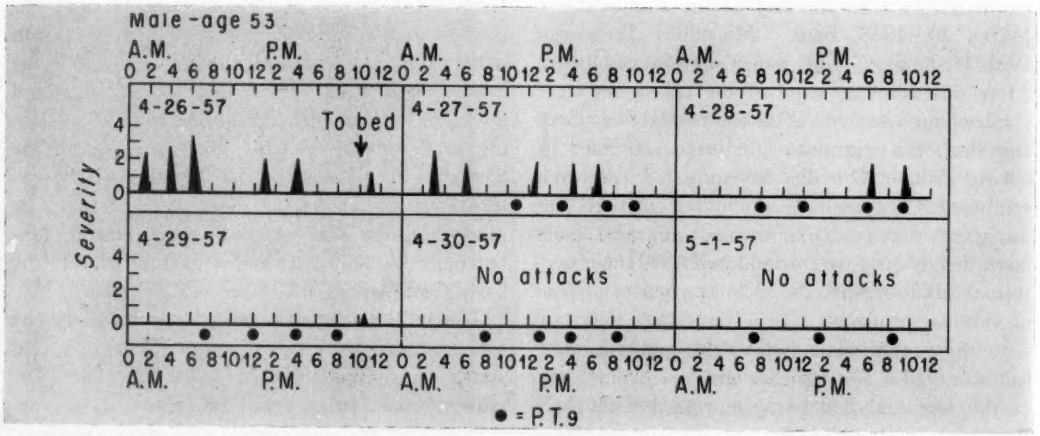


Fig. 4

The number and severity of attacks of right histaminic cephalgia. Patient was having from five to six attacks every twenty-four hours at the time he was admitted to the hospital. Treatment with beta (2-pyridyl) ethylmethylamine hydrochloride (PT-9) was instituted on April 26, 1957, with 1 milligram four times daily. The attacks ceased in forty-eight hours. They recurred two weeks after he returned home, persisted for four weeks, then ceased for sixteen months.

The Clinical Picture

Character and distribution of pain—Histaminic cephalgia is characterized by frequent and severe, but short, attacks of unilateral head pain. They generally last less than an hour. The pain, which usually commences suddenly and often terminates suddenly, tends to awaken the patient at night one or two hours after he has gone to sleep (figs. 3 to 5). Day attacks are not infrequent, however (fig. 3).

Pain is the patient's outstanding complaint. During a severe attack it is constant, excruciating, burning, and boring. It is unilateral, involving the eye, the orbital area, the maxilla, the temple, and frequently extending to the upper jaw, roof of the mouth, and occipital area. Occasionally it extends to the ear and to the lower jaw, neck, and shoulder.

In the typical full-blown attack (figs. 1 and 2), the pain is associated with profuse congestion and watering of the eye, stuffiness or rhinorrhea of the nostril, and frequently swelling of the temporal vessels on the affected side. Orbital edema and sweating of the forehead on the involved side occur often. The affected side may be sore for a while after the attack has ceased.

At the height of the pain, the pulse rate of a few patients decreases from 70 to 45 or 50 beats per minute. As the pain lessens and disappears, the pulse rate returns to its normal level. Convulsive seizures also may occur at the height of the pain. I have seen them in at least five patients. Extensive investigation disclosed no cause for the convulsions. Attacks tend to occur in a series and may appear to be seasonal; I seemed to have had more patients under observation during August and September than in other months. Horner's syndrome is common; it may disappear after a given series of attacks have ceased or may persist indefinitely.

Histaminic cephalgia occurs more frequently and with greater severity in men than in women.

Suicide contemplated—So severe and frequent are the attacks of pain that almost every patient has, at times, contemplated committing suicide; but I have never known one to do so, probably because of the short duration of the attack and because he feels normal between attacks. The condition is sometimes referred to in the literature as "suicide headache."

Night attacks—Night attacks, which awaken a patient from sleep, are characteristic of this illness. No other pain syndrome, as far as I am aware, occurs during sleep with such clocklike regularity. Pain often occurs at the same time night after night and it is usually severe enough

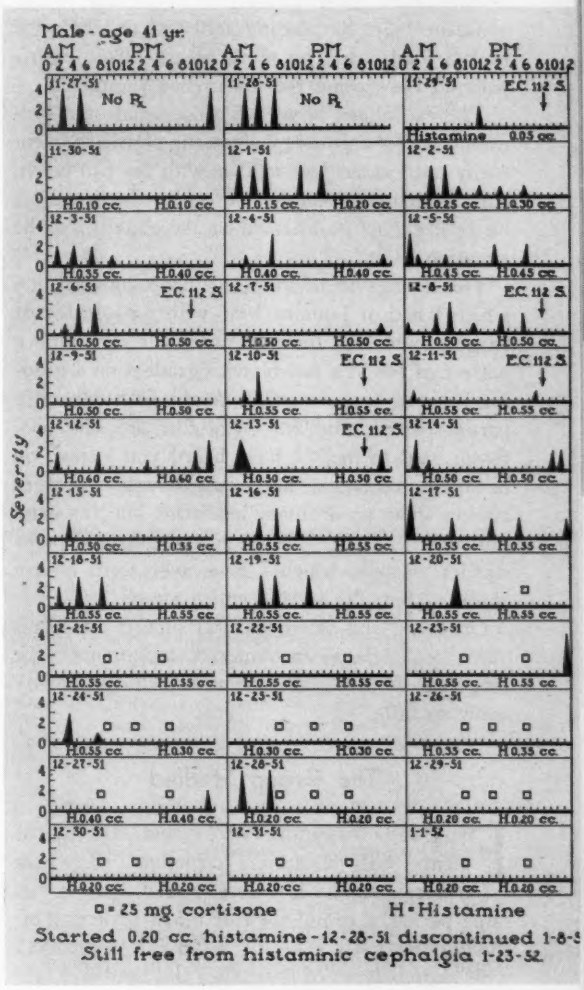


Fig. 5

The frequency and severity of attacks of histaminic cephalgia. The clinical course of the illness; the dosage of histamine, which was given subcutaneously twice daily; the other drugs employed; and the patient's response are clearly indicated. When E.C. 112 S. (ergotamine with caffeine suppositories) was employed at bedtime, attacks of histaminic cephalgia were blocked for twelve to twenty-four hours. The patient did not respond to histamine when the dosage reached 0.55 cubic centimeter twice daily, but did respond when the dosage was reduced to 0.2 cubic centimeter twice daily and combined with 75 milligrams of cortisone a day. He had been free from pain for four days at the time of dismissal.

to make the patient jump out of bed or even to bang his head against the floor or wall.

Many of my patients have said, "I'm afraid to go to bed at night," and have tried to avoid the nocturnal attacks by sleeping in a chair; but they have rarely succeeded.

Remissions and exacerbations—These occur spontaneously. Succeeding series of attacks seem to last longer and be more severe. Most of my patients have come for emergency treatment.

The full-blown attack—To appreciate the syndrome of histaminic cephalgia, the physician eventually must come face to face with the full-blown clinical picture. When he does so for the first time, he is likely to be alarmed at the gravity of the situation.

This brings to mind a telephone conversation which I had in January 1956 with a professor of surgery, who, for the first time, was observing a patient of his in a full-blown (grade 4 on a grading basis of 1 to 4) attack on the fifth day after partial gastrectomy for pyloric ulcer. The professor said to me, "I have heard you lecture on histaminic cephalgia, but I just thought you were talking about an ordinary headache, but this is no ordinary headache. It is the most dramatic demonstration of pain which I have ever seen. I have observed him during the entire attack."

Once the full-blown clinical picture of histaminic cephalgia is encountered, it will never be forgotten. It is a syndrome about which so many know so little.

The Group Studied

From 1937 through 1957, I studied 1,402 patients with histaminic cephalgia, of whom 1,226 were men and 176 were women. During this same period, a grand total of 6,516 patients (including the 1,402 cases of histaminic cephalgia) with various types of headaches and head and face pain were studied. These patients were under observation in my laboratory for varying lengths of time. Of the many types of headache studied, histaminic cephalgia seemed to me to be the most clear-cut clinical entity, lending itself well to laboratory study.

The clinical picture of histaminic cephalgia must be accurately defined if valid conclusions are to be drawn from the observations which I wish to report. In doing so, I am attempting to describe only what I have seen and what my patients have told me. I have included reports of 13 patients to illustrate the various points.

My First Case of Histaminic Cephalgia

CASE 1

I observed and carefully studied my first case of histaminic cephalgia in 1937. It was largely by accident that I did so.

A woman, 37 years old, had come to the Mayo Clinic complaining of attacks of severe pain on the right side of the head and face. These episodes came at night with clocklike regularity, usually awakening her between 3 and 4 A.M.

Routine examinations, including a careful neurologic examination, had produced negative results. The neurosurgeon seeing her in her final consultation was ready to dismiss her, but she rejected the idea of going home. She related, "Night after night I go to bed feeling perfectly normal and fall asleep; and then about 3 o'clock in the morning, and without any apparent cause, I am awakened with this agonizing pain which makes me get out of bed. It is the same thing night after night. I was having this pain before I came here and am still having it. In spite of the many attacks which I have had, no doctor has ever observed me in one of these spells." The neurosurgeon then telephoned me, explained the patient's symptoms, and added that he would like to send her to me for further studies.

The following morning, in my laboratory, she told me her story and vividly described the attack of the previous night. I listened, but I could not at that time fully appreciate her story. Day after day she came in and described her experiences of the night before. I had asked her to make careful notes concerning each attack, hoping that they might give me a clue as to the nature of her illness.

She was living in a hotel, and the short duration of night attacks did not permit me or my assistants to reach her in time to observe an attack. Finally, she recalled having had an attack during the day at the clubhouse after she had finished a game of golf. She wondered if it had been provoked by a cocktail. This was the clue I had been looking for.

Origin of the histamine provocative test and histamine desensitization—With the patient under controlled environmental conditions (without food and with the room at 78° F. and 40 per cent humidity), I gave her 1 ounce of alcohol by mouth. Forty-five minutes later, an attack of severe pain developed in the right side of the head, the pain being similar in every respect to a spontaneous attack. The surface temperature of the right temporal region was 3.2° F. higher than that of the left.

It then occurred to me to try histamine as a provocative agent. The subcutaneous injection of 0.5 milligram of histamine base precipitated another attack. In order to study the various phenomena associated with the attacks, the same quantity was given on several days. Succeeding attacks seemed progressively less severe and more difficult to precipitate.

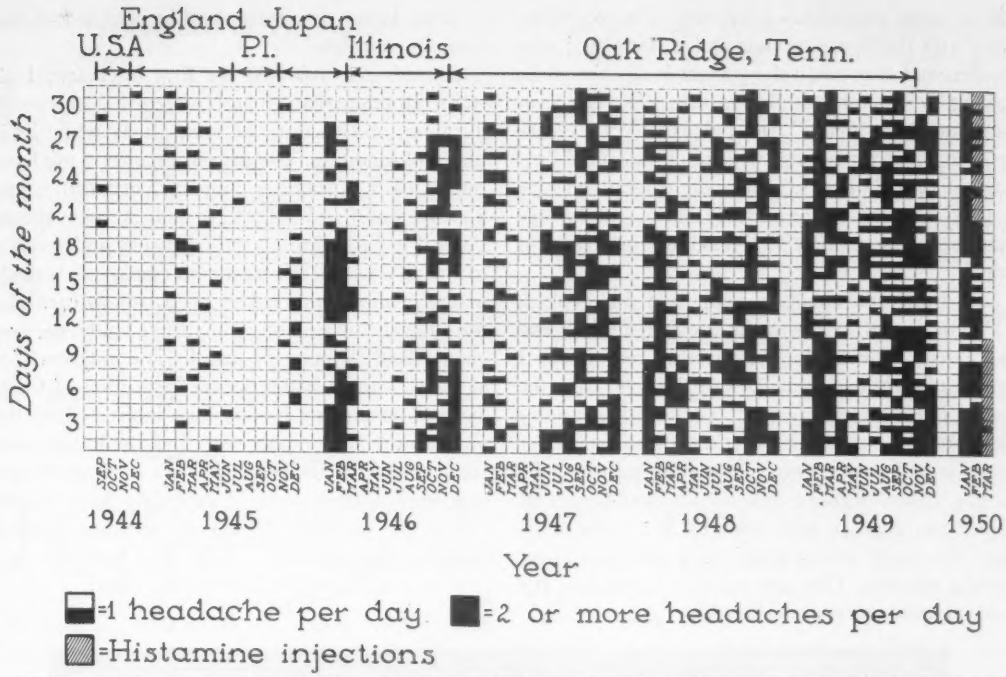


Fig. 6

The number and frequency of attacks of right histaminic cephalgia in a man, aged 39, since the original onset in 1944. He had been unable to work since November 1, 1949. When he came to the clinic and was hospitalized for emergency treatment on February 18, 1950, he was having attacks both day and night; average duration was forty minutes. Alcohol, including beer, always provoked attacks. Nicotinic acid, cafergone (2 to 4 tablets daily), antihistaminics, and intravenous histamine therapy had not helped. A histamine provocative test (0.35 milligram of histamine base) caused a typical attack of right histaminic cephalgia in fifty-eight minutes. The intravenous administration of 1 cubic centimeter of D.H.E.-45 gave relief of pain in ten minutes. Subcutaneous histamine desensitization was started immediately, twice daily, as indicated in the graph, and continued for eighteen days. Attacks ceased after the seventh day of treatment. He was taking 0.25 cubic centimeter of histamine twice daily at the time of dismissal, March 9, 1950. He wrote on March 23, 1957, that he had been able to alter the histamine dosage and completely control the few recurrences.

After several injections, the histamine seemed to lose its power to produce the pain. It occurred to me that the gradually increasing resistance to histamine might in some way alter the phenomena of vasodilation intrinsically associated with the appearance of pain in the spontaneous headaches. In this manner, the histamine provocative test and the histamine desensitization treatment for this type of headache had their origin. This patient obtained complete relief of her headaches with histamine therapy.

During the course of several induced attacks and one spontaneous attack of right head pain, I noted that compression of the right common carotid artery would stop the pain. The pain promptly recurred when pressure was released. These attacks were aborted either by the subcutaneous injection of 10 minims (0.61 cc.) of epinephrine (in 1:1,000 solution) or by the intravenous administration of epinephrine (in 1:200,000 solution).

Diagnosis. After many detailed studies, I noted on September 24, 1937, "This looks like migraine or erythromelalgia of the right external carotid artery."

Course. In 1943, approximately six years later, attacks of right histaminic cephalgia recurred, whereupon the patient returned. She responded to subcutaneous histamine desensitization, and in August, 1959, she reported that she had never had another attack of that agonizing pain.

In 1937 I could not realize that this case was the beginning of a study which would last a lifetime or that the headache which I was studying was destined to become designated in Dorland's Medical Dictionary as "Horton's headache or syndrome." The clinical picture is now clear.

Taking the History and Making Records

Leading Questions—To record a detailed history requires time and patience, but it gives more clues to the nature of the patient's headache than

do all other procedures combined. The record begins with the first interview and is completed only at the final one, when the patient is dismissed. In taking the history, I always ask, "Do you ever have attacks at night?" And I also instruct, "Please tell me about the attacks which you have had during the past 24 hours." Since the patient can give a good account of the past 24 hours, the history can be more accurately developed by working backward.

To these questions, a man, age 54, replied, "Practically all of my spells occur at night," and he added, "During the past twenty-four hours I have had eight bad spells; six of the eight were the worst I've ever experienced. They always involve the left side of the head, they come on rather rapidly, and within two minutes the pain is at its height. It lasts eight or nine minutes and tapers off in another eight or nine minutes. It's really terrible. The spells are all alike; each one lasts about twenty minutes. They are not sick headaches. It's just a terrible pain in my head."

What better description can be obtained of histaminic cephalgia!

Graphic Records—At the first interview, I always tell the patient to keep a record of the onset, duration, and severity of each attack while he is under observation. The patient reports to my laboratory daily, including Sundays, between 8 and 9 A.M. and 4 and 5 P.M. A daily graphic record (figs. 3 to 5) indicating the frequency and severity of the attacks and the treatment employed, is made of each patient and enables me to follow carefully the clinical course. For comparative study, the frequency and severity of attacks are indicated for at least 24 to 48 hours before institution of treatment. The patient becomes as interested as the physician in the graphic record and will cooperate fully in making the recorded data accurate. Many engineers with histaminic cephalgia have helped evolve the method of making accurate graphic records (figs. 6 and 7), which have been of great help in evaluating the therapeutic effort.

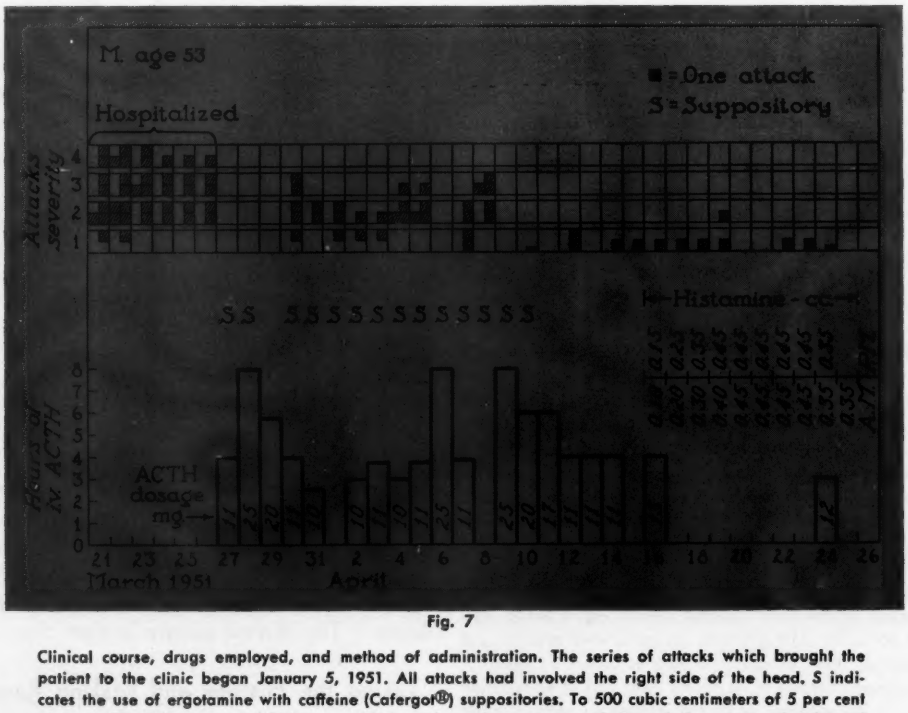


Fig. 7

Clinical course, drugs employed, and method of administration. The series of attacks which brought the patient to the clinic began January 5, 1951. All attacks had involved the right side of the head. S indicates the use of ergotamine with caffeine (Cafergot®) suppositories. To 500 cubic centimeters of 5 per cent glucose, 25 milligrams of ACTH was added; and varying amounts of the solution were administered intravenously at the rate of 20 drops per minute for three to eight hours daily. The daily dosage of ACTH is indicated. The frequency and severity of attacks decreased. Subcutaneous administration of histamine instituted on April 16 stopped the attacks after April 24. A year later the patient was still free from attacks.

Examination of the Patient

COMPLETE PHYSICAL AND NEUROLOGIC examinations and routine laboratory tests should be performed. The eyes, ears, nose, and throat should be examined carefully. Roentgenographic examinations of the head should be employed routinely in all cases of headache. Special diagnostic tests may be indicated also when certain organic lesions are suspected.

Since these examinations and tests almost invariably give negative results, the physician is still confronted with the patient and his pain. How can he best arrive at a correct diagnosis?

Differential Diagnosis

THE PHYSICIAN SHOULD have no great difficulty in distinguishing histaminic cephalgia from other types of head and face pain. The many physicians with histaminic cephalgia whom I have observed and treated certainly know the difference between histaminic cephalgia and migraine, even if some writers do not. One professor of neurology remarked, "Histaminic cephalgia is the most clear-cut clinical entity in medicine. I ought to know, I've had it." As said before, the clinical history gives the best clue to the diagnosis. The fact that approximately 40 per cent of my patients with histaminic cephalgia have undergone various major and minor surgical operations in an attempt to obtain relief of their pain indicates the need of a clearer conception and a better understanding of the various pain syndromes involving the head.

Migraine—In migraine there are three phases to consider; whereas in histaminic cephalgia there are only two. In migraine, the first phase is associated with vasoconstriction (which accounts for the scotomas and cortical manifestations) and is not accompanied by pain. This phase does not occur in histaminic cephalgia. The second phase in migraine is ushered in by vasodilation, which is the immediate cause of the pain; this phase is common to the two syndromes, but develops more promptly in histaminic cephalgia than in migraine. The third phase, the edematous phase, is associated with pain and is common to both syndromes. It is of short duration in histaminic cephalgia, but may persist for hours in migraine.

Heredity plays little or no role in histaminic cephalgia. Nausea, vomiting, and cortical phenomena are usually absent. During a given series of attacks, the pain always occurs in the same area and does not shift from side to side as it often does in migraine. Sustained contraction of the cervical muscles usually plays a prominent part in the attack of migraine but is usually absent in histaminic cephalgia. Histaminic cephalgia occurs chiefly in men, whereas migraine occurs chiefly in women. The patient with migraine usually refers to the pain as "sick headache," whereas the patient with histaminic cephalgia always refers to it as "head pain"; he does not think of it primarily as a headache.

Trigeminal neuralgia—This pain, which is always sudden, severe, and lancinating, always follows the distribution of one or more of the branches of the trigeminal nerve. Trigger zones are present. Bilateral pain is unusual. The pain of histaminic cephalgia does not follow the anatomic distribution of any cranial nerve. The pain pathways of histaminic cephalgia have not been worked out completely (18).

Sphenopalatine ganglion neuralgia and vidian neuralgia (19)—Although these terms are frequently encountered in medical literature, it is extremely doubtful whether inflammation of the sphenoid sinus or sphenopalatine ganglion can produce the original pain pattern described by Sluder (20) in 1908. Vail (21), in 1932, stated that involvement of the vidian nerve rather than the sphenopalatine ganglion accounted for the pain pattern described by Sluder. It now seems more likely that so-called sphenopalatine ganglion and vidian neuralgias actually are vasodilating syndromes that involve the internal maxillary artery, especially the third portion that supplies this area. The pain is vascular in origin.

Petrosal neuralgia—Gardner, Stowell and Dutlinger (22) stated that the syndrome which they termed "petrosal neuralgia" was originally described by me as histaminic cephalgia, or Horton's syndrome. They assumed that parasympathetic impulses over the petrosal nerve caused unilateral lacrimation, unilateral swelling and secretion of the nasal mucosa, and unilateral head pain. Their treatment consisted of cutting the superficial petrosal nerve on the involved side. This procedure will be referred to later in this paper.

Atypical facial neuralgia—This term (23) has been used to describe a peculiar, deep-seated, aching pain that is neither constant nor paroxysmal

but occurs in attacks of varying severity. Remissions are rare. In my experience, atypical face pain usually does not have a vascular component but often appears to have a psychogenic basis. The pain does not follow the distribution of any cranial nerve. It is less severe than trigeminal neuralgia and is likely to be more constant. It may begin at any age, whereas trigeminal neuralgia and histaminic cephalgia tend to develop later in life.

Ophthalmoplegic migraine—In ophthalmoplegic migraine, the ocular phenomena occur during the first and second phases of the attack, whereas the ocular phenomena in classic migraine are limited to the first phase. Ophthalmoplegic migraine usually involves the third cranial nerve, and, occasionally, the fourth and sixth cranial nerves. Ptosis of the eyelid occurs. Angiographic studies did not reveal intracranial aneurysms in the few cases I have studied. These forms of migraine are rare in my experience, but they do occur and may or may not be associated with intracranial organic disease. The duration of an episode of ophthalmoplegic migraine is likely to be longer than that of classic migraine. Ocular paralysis may persist for several days after the pain has ceased.

Sinusitis—The pain is dull and constant; it may be unilateral or bilateral, depending on the sinuses involved. There is tenderness to pressure over the involved sinuses. The appearance of the inflamed nasal mucous membrane and the presence of nasal discharge, nasal congestion, and edema should permit sinusitis to be distinguished from histaminic cephalgia. The fever and positive x-ray findings help to make the differential diagnosis relatively easy.

Tension headache—Patients who have tension headaches are of all ages. They often have exceptional ability, having failed in life in one respect only; namely, in learning to relax. In some patients, the pain may be due entirely to sustained contraction of the cervical and scalp muscles; but in the majority, there is also a vascular component. The chronic overstretching of extracranial vessels may give rise to more pain than the sustained contraction of the skeletal muscles. The pain may involve the entire head, but it is likely to be more intense in the occipital region. It is not as excruciating as in migraine, and gastric disturbances rarely accompany it. Underlying emotional disturbances are always present to some degree. Some observers regard myalgic headache, indurative headache, nodular headache, rheumatic headache, and spastic myalgia as synonymous with tension headache.

Periarteritis of the temporal artery—This rare condition should be mentioned, for it must not be confused with temporal arteritis.

CASE 2

In December 1952, I saw a married woman, 31 years old, who complained of left temporal pain of two years' duration. When the pain first developed, it occurred at fairly frequent intervals with free periods between attacks. The free days became less frequent, and the pain had been constant throughout the waking hours for the six months prior to admission to the clinic. Sneezing or coughing seemed to accentuate the pain. When the pain was severe in the left temporal region, she occasionally had noted slight pain in the right temporal region also. On two occasions, local injection of procaine around the left temporal artery had stopped the pain for two to three hours. Both temporal arteries pulsated normally, but the left one was tender to palpation. When the left common carotid artery was compressed and suddenly relieved, the pain in the left temporal artery was momentarily accentuated. Breathing of 100 per cent oxygen with a BLB mask did not stop the pain or prevent accentuation when the patient coughed. All other examinations and the various laboratory studies gave negative results.

Injection of 1.3 cubic centimeters of a 2 per cent solution of procaine around the left temporal artery gave complete relief for eighty minutes. Several days later, a portion of the left temporal artery which seemed thickened along its entire course was removed. The pathologist reported periarterial fibrosis, grade 2 plus, which involved the adventitial coat of the vessel. The medial and intimal coats of the artery were normal. The patient was free from headache at the time of her dismissal three days later.

I later made similar observations in a man aged 33.

Temporal arteritis (24, 25)—This is a medical emergency because of the ocular involvement which occurs in more than half of the patients, ranging from diplopia to complete blindness. Sudden loss of vision in an elderly patient with headache and symptoms of sepsis should alert the physician to the possibility of temporal arteritis. The disease occurs exclusively in older people, the average age being 69.2. Severe headache, which is present throughout the waking hours, difficulty in chewing (intermittent claudication), general malaise and lassitude, symptoms of sepsis, anemia, and a high sedimentation rate may persist for weeks before the typically swollen temporal arteries appear. These are the foremost clinical fea-

Table 1
Provocative Tests of Right Histaminic Cephalgia in One Patient

Date	Time	Agent employed	Attack			
			Induced	Severity, grade	Onset, minutes after injection	Duration, minutes
8–2–49	11:25 a.m.	0.35 cc. of normal saline subcutaneously	No			
8–2–49	3:24 p.m.	0.35 mg. of histamine base subcutaneously	Yes	1	36	15
8–3–49	4:04 p.m.	1/50 grain of nitroglycerin sublingually	Yes	3	41	24
8–4–49	9:05 a.m.	100 mg. of nicotinic acid subcutaneously	No			

tures of the disease. Biopsy of the temporal artery invariably shows giant cell arteritis.

Unilateral recurrent erosion of the cornea (4)—Unilateral recurrent erosion of the cornea, which is rare and which occurs at night or on opening the involved eye in the early morning, may be mistaken for histaminic cephalgia. The pain, however, is confined to the orbit and is associated with blepharospasm, photophobia, and a sensation suggesting a foreign body in the eye. Examination of the cornea with the slit lamp during the attack will reveal erosions, which may not be in evidence an hour or so later. This condition is easily overlooked.

CASE 3 (4)

One of the first cases I encountered was that of a 43-year-old physician who had had attacks of pain in the right eye for eighteen months. A number of ophthalmologists, on examinations between bouts of pain, had reported the right eye as normal. He was sent to me because histaminic cephalgia seemed likely. During the pain, he had the sensation of having a foreign body in the eye. Between attacks the eye felt normal. The right eye was bandaged at bedtime so that he could not open it. Upon removal of the bandage the next morning, the pain developed immediately. The cornea was stained with fluorescein and examined by means of a slit lamp. The epithelium in the lower half of the cornea was stained. The whole cornea appeared edematous. At another examination during the course of an attack of pain, similar superficial erosions were observed.

The Provocative Test

Purpose—Although provocative agents are not specific for various types of headaches, they give valuable help to the physician in arriving at a correct diagnosis. Reproduction of an attack of histaminic cephalgia with its subsequent abortion, although not always possible, is of great value to the patient and to the physician. It permits the physician and the patient to have a common understanding of the pain problem. Error in diagnosis and failure of treatment occur largely because the physician has not had the opportunity to see the patient during a spontaneous or induced attack of pain in the head.

In the induced attack, the physician is primarily concerned with the exact reproduction of the location, distribution, and character of the pain and with its associated phenomena, rather than with its intensity.

Abortion of Induced Attacks—When it is evident that the induced attack corresponds exactly to spontaneous attacks, the physician should institute measures for promptly aborting it. If the induced

attack is permitted to continue until the pain reaches its maximal intensity, he may have great difficulty in controlling it. The intravenous administration of 1 cubic centimeter of dihydroergotamine (D.H.E.-45) is the most satisfactory agent for aborting induced attacks (cases 6 and 7). Other vasoconstricting agents, such as 100 per cent oxygen given by mask, are helpful and may be used in combination with the intravenous administration of dihydroergotamine.

Therapeutic agents which relieve induced attacks may guide the physician in future management. The ability to reproduce an attack of head pain identical to the patient's previous spontaneous attacks and to terminate it abruptly within a minute or two heightens the patient's confidence in the

Table 2
Provocative Test of Right Histaminic Cephalgia on a Man, 35 Years Old*

Time, p.m.	Blood Pressure, mm. Hg		Pulse, rate	Remarks
	Systolic	Diastolic		
3:09	139	70	80	
3:10	138	70	100	
				0.35 mg. of histamine base subcutaneously
3:11	138	70	98	Physiologic effects Face flushed
3:13	138	70	97	
3:14	138	70	96	
3:15	125	60	99	Dull pain in fronta: region
3:20	125	60	98	
3:25	125	69	79	
3:30	139	69	75	
3:35	120	60	75	
3:40	122	60	75	Color normal
3:45	115	55	65	
3:50	115	56	60	
3:55	121	57	68	
4:00	115	58	68	Feels normal (latent period)
4:05	119	58	68	Pathologic response Sharp throbbing pain in right frontal region
4:10	115	80	60	Redness and tearing of right eye
4:13				Severe pain in right frontal region
4:15				100% oxygen given by B&B mask
4:25				1.0 cc. of D.H.E.-45 intravenously
4:32				No pain

* The induced attack of right histaminic cephalgia, which developed at the end of 55 minutes, was identical to his previous spontaneous attacks.

Table 3
Provocative Test: Cocainization of Sphenopalatine Ganglion During Latent Period in an Attempt to Prevent Histamine-Induced Attack

Minutes after injection	Result
Subcutaneous injection of 0.35 mg. of histamine base	
10	Premonitory symptoms
20	These faded; felt normal. Left sphenopalatine ganglion cocainized
35	Grade 4 attack of histaminic cephalgia developed

physician, thus creating the ideal physician-patient relationship.

Agents, Doses, and the Response—I have used many agents in an attempt to provoke a headache which would match that described by the patient (tables 1 to 4) and usually have succeeded in doing so. References have been noted in the early literature to the relationship of ingestion of *alcohol* to the headache. Approximately 45 per cent of my patients with histaminic cephalgia noted that alcohol would precipitate attacks during a given series of attacks. The majority, however, found that it would not precipitate an attack during remissions between two series of attacks.

Histamine base administered subcutaneously in a dose of 0.35 milligram is the best provocative agent (tables 2 and 3), having tripped the mechanism in approximately 69 per cent of my patients. This amount does not produce undue discomfort; larger doses are, as a rule, unnecessary.

The patient undergoing this test should lie on a comfortable couch in a quiet atmosphere. He should be under observation for an hour or longer. The blood pressure and pulse rate should be recorded, as in tables 2 and 4. The patient need not know that he is undergoing any special test.

"Histaminic cephalgia" and "histamine headache" should not be regarded as synonymous. The immediate reaction after the administration of histamine as a provocative agent is a generalized histamine headache, which is a physiologic response. It lasts five or ten minutes or even longer, and it occurs in normal persons as well as in those who have histaminic cephalgia. Thereafter, for a period of a few minutes, the patient frequently feels normal. In the majority of patients with histaminic cephalgia, however, a typical attack occurs fifteen to fifty minutes after cessation of the histamine headache. This may be regarded as a pathologic response. In some patients, a latent period does not occur; and the provoked attack of histaminic cephalgia develops as the physiologic effects of drug cessation. I have never been able to provoke an attack of histaminic cephalgia in a normal person.

The pain of histamine headache is chiefly intracranial in origin, due to dilatation of the large vessels at the base of the brain; whereas the pain of histaminic cephalgia results chiefly from dilatation of the extracranial vessels.

What happens during the latent period in histaminic cephalgia? Why does a latent period occur in most cases but not in all? What is its significance? I have often wondered, but I do not know the answers. It is instructive to note that an otolaryngologist cocainized the sphenopalatine ganglion area on the involved side (table 3) during the latent period, but this did not prevent the development of the attack of histaminic cephalgia in the usual length of time.

The histamine provocative test has been positive even on patients who have had certain major surgi-

cal procedures carried out in an attempt to obtain relief from their pain. For example, I have been able to provoke attacks in patients after ligation of the temporal and external carotid arteries, section of the greater superficial petrosal nerve, cervical sympathectomy, and even after the intracranial

Table 4
Previous Stellate Ganglion Block Failed to Abort Induced Attack of Histaminic Cephalgia (Case 7)

Time, a.m.	Blood pressure, mm. Hg		Pulse	Remarks
	Systolic	Diastolic		
9:29	140	80	100	Patient felt normal
9:30	0.4 mg. histamine base given subcutaneously			
9:32	140	80	100	
9:34	130	70	90	Face flushed, grade 3
9:36	122	68	93	
9:38	130	70	93	
9:40	130	70	92	
9:42	125	70	95	Flush fading
9:44	130	70	95	
9:46	126	70		Patient feels all right
9:48	140	70	100	
9:50	140	70	95	Pain in right temporal area
9:52	150	70	95	Pain in right upper teeth
9:54	150	70	100	Right eye red and tearing
9:56	140	70	100	Typical right histaminic cephalgia
9:58	140	70	95	15 cc. of PAB_3* injected C_7 to T_1 on right side
10:00	140	70	91	
10:02	140	70	90	
10:04	140	70	88	
10:06	140	70	88	5 cc. of PAB_3 injected from C_7 to T_1 on right side
10:08	130	70	88	
10:10	130	70	82	10 cc. of PAB_3 injected from C_7 to T_1 on right side
10:12	130	70	80	
10:14	130	70	82	Right side of forehead dry; sweating on left side of forehead; right Horner's syndrome
10:16	130	70	78	No relief of histaminic cephalgia
10:22				Right hand 4° F. warmer than left; complete Horner's syndrome and right pupil smaller than left with ptosis of right upper lid

* Procaine hydrochloride, ammonium sulfate and benzyl alcohol.

section of the trigeminal nerve, as in case 8. In this case, the pulsating histamine headache developed on the right side of the head, where the right trigeminal nerve was intact, but not on the left side, where the trigeminal nerve had been sectioned. The pain on the right side developed promptly, persisted for five minutes, and was followed by a latent period of ten minutes; the histaminic cephalgia attack developed on the left side twenty-six minutes later. This seems to illustrate the difference between histamine headache, which is intracranial in origin, and histaminic cephalgia, which is extracranial in origin.

I have never been able to reproduce an attack of histaminic cephalgia with *nicotinic acid.*

The sublingual administration of 0.0013 gram of glyceryl trinitrate will precipitate an attack of histaminic cephalgia in many patients with this illness.

The time required for the histamine test is less than that for the nitroglycerin test. The attack induced by histamine usually occurs in forty to forty-five minutes, whereas that after nitroglycerin occurs in approximately seventy-five minutes. In my experience, it is easier to control the attack induced with histamine than one induced with nitroglycerin. Hence, I consider histamine the provocative agent of choice.

A negative histamine provocative test does not rule out the presence of histaminic cephalgia. Such results may be explained in certain cases by a period of unresponsiveness to provocative agents that follows use of ergotamine products, for example, to terminate a spontaneous attack. It is well to inquire before the test whether the patient has been taking such drugs. Then, too, a refractory period often follows a spontaneous attack, during which time an attack of headache cannot be precipitated. The refractory period varies with different patients. In the "free period" between series of attacks of histaminic cephalgia, which often last for many months, provocative tests usually give negative results.

Etiologic Aspects

HISTAMINIC CEPHALGIA represents a localized anaphylactoid reaction with both local and systemic manifestations. Patients with histaminic cephalgia are hypersensitive to histamine. The attacks can be reproduced so accurately that patients are unable to distinguish between induced and spontaneous attacks. Not only is the histamine provocative test a diagnostic procedure, but it should be regarded as a form of localized shock therapy at the cell level.

The exact mechanism by which this syndrome is produced is not clear. Experimental and clinical data indicate a local release of histamine from sensitized cells in the pain area, with resultant vasodilation confined, for the most part, to the ramifications of the external carotid artery. During induced and spontaneous attacks, with patients under controlled environmental conditions, the surface temperature of the involved side of the head invariably rises more rapidly and to a higher level than that of the opposite side of the head. This obviously indicates local vasodilation. During spontaneous and induced attacks, the acidity of the gastric contents increases to an abnormally high level, indicating absorption of "released histamine" from sensitized cells into the blood stream. This increase in acidity is comparable to that which is induced by the subcutaneous injection of known amounts of histamine (3, 6). It cannot be accurately reproduced by so-called stress factors. Endogenous histamine released anywhere in the body will stimulate gastric secretion, even when the amounts liberated are so small that they cannot be detected in the blood. I have called attention to the relationship between acute peptic ulcer (3) and histaminic cephalgia, but I have not observed this relationship in cases of migraine (26). In addition to histamine, other biologic agents, perhaps serotonin and heparin, are liberated from sensitized cells (mast cells?) at the site of pain.

Punch biopsy of the skin from both temporal areas in three patients* (pain area and control area) during the course of induced and spontaneous attacks of histaminic cephalgia have not revealed changes in the number or appearance of mast cells comparable to that reported in the experimental animal. Cells grudgingly give up their secrets. Unfortunately the "shocked" mast cells were not examined under the electron microscope. When they are finally examined under the electron microscope, I predict that they will show comparable changes to those in the experimental animal. More work needs to be done in this field.

Perception of pain and the histamine content of

*Work done with Drs. Hamilton Montgomery and R. R. Kierland.

the skin in man, as well as in the guinea pig, appear related. In 100 (27) normal, healthy students, sensitivity to pain was three times more acute in the retroauricular regions, where the histamine content of the skin was high, than in the volar surface of the thumb, where the histamine content of the skin was relatively low. Histamine is the chemical mediator of cutaneous nerve endings.

Histamine Skin Tests

Wheal and flare—The question has often been asked, do histamine skin tests give the physician accurate information concerning the patient's sensitivity to the drug? These tests, if carried out under controlled environmental conditions with the patient in a basal state (that is, without food in the stomach), have great scientific interest; but their practical value is questionable. When a small amount of histamine is injected into the skin, a wheal and surrounding flare promptly develop. Histamine produces (1) local dilatation of the capillaries and venules by direct action; (2) widespread dilatation of surrounding arterioles from a local axon reflex; and (3) local increased permeability of the walls of the minute vessels, increased exudation of fluid, and wheal formation.

The size of the flare resulting from the intracutaneous injection of varying amounts of histamine is determined more by the environmental temperature than by the actual sensitivity of the patient. For example, the flare is likely to be more than twice as large if the test is carried out in a temperature of 85° F. than in a temperature of 65° F.

Browne (28), while working in my laboratory 20 years ago, used the decrease in the size of the wheal and flare following the intracutaneous injections of histamine of varying dilutions as an index to the patient's response to histamine desensitization. Tests were carried out in an environmental temperature of 78° F. and 40 per cent humidity. The dilutions of histamine employed were 1:100,000, 1:1,000,000, 1:4,000,000 and 1:8,000,000. The flare disappeared completely in 45 per cent of the 23 patients with histaminic cephalgia who were treated by means of histamine desensitization; in 25 per cent it was significantly reduced (fig. 8), while in 30 per cent it did not change significantly. The results of treatment and the state of histamine flares were related. Since formation of the flare depends on the axon reflex, the daily injections of histamine in some way altered this mechanism. The desensitization phenomenon apparently persists for only a few weeks before the axon reflex reverts to its former state. The 1:100,000 dilution of histamine was the most useful dilution employed in this study.

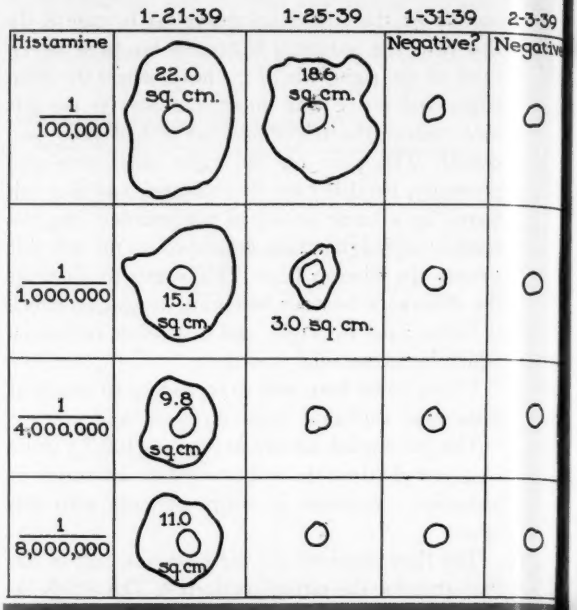


Fig. 8

Skin reactions as an index to desensitization to histamine. The patient, a woman, aged 62, had had attacks for five years. The size of the wheal and flare, using various dilutions of histamine, with the patient in a basal state under controlled environmental conditions and before histamine desensitization was instituted, is indicated in the squares beneath the date, January 21, 1939. Histamine treatments were given twice daily. The histamine flares completely disappeared during treatment. No change occurred in the histamine wheal. The patient obtained complete relief of histaminic cephalgia.

Control study—Normal subjects were tested in the same manner, with the same dilution of histamine, over a comparable period of time; but they were not treated with histamine desensitization twice daily. Their flares did not change significantly. No change occurred in the wheal in either the treated subjects or the control subjects. Much more work needs to be done in this field.

Approach to the Treatment

GOOD RAPPORT BETWEEN the patient and the physician is important in the treatment of histaminic cephalgia. Most of my patients with his-

taminic cephalgia have come for emergency treatment, having been incapacitated by their illness. Any strong-hearted individual who has been awakened from sleep with agonizing head pain night after night for a prolonged period, who has visited many physicians and medical centers, and who has had numerous surgical operations in a vain attempt to obtain relief, is likely to be confused and bewildered by his illness.

In treating the headache, I must treat the patient, not merely the headache alone. When shaking hands with the patient for the first time, I always try to make the patient aware that I am deeply interested in his headache problem and that I will try in every way possible to help him. In the first interview I try to initiate a warm doctor-patient relationship. This is the foundation for any type of treatment which may follow. It is made easy if the physician is fortunate enough to see the patient at the beginning of a severe attack of histaminic cephalgia and promptly administers dihydroergotamine intravenously. The attack will be aborted so quickly that the patient will think a miracle has happened.

The physician's attitude must be friendly, sympathetic, tolerant, and flexible at all times. To achieve success in the management of the patient, he must be anatomically, physiologically, pharmacologically, and psychiatrically curious.

Treatment: A Medical Not a Surgical Problem

HISTAMINIC CEPHALGIA is a medical, not a surgical, problem; yet roughly 40 per cent of my patients had undergone operative procedures for their pain.

At the height of the attack, most patients have a plugging of the nostril and rhinorrhea on the involved side. This suggests sinusitis to the unwary otolaryngologist and apparently accounts for numerous unnecessary intranasal operations and, sometimes, multilating procedures on the sinuses. When the pain spreads into the upper jaw, teeth are frequently extracted.

Many patients have discovered that compression of the distended temporal vessels gives momentary relief, an observation sooner or later confirmed by the physician. Ligation of the temporal artery as a therapeutic procedure follows all too often. One man told me that on his way from the operating room, he suffered an attack of the same pain as before the ligation. Another patient had an attack less than 50 hours after ligation of a temporal artery. The surgeon then reasons, I presume, that perhaps the operation was not extensive enough; and he then ligates the external carotid.

CASE 4

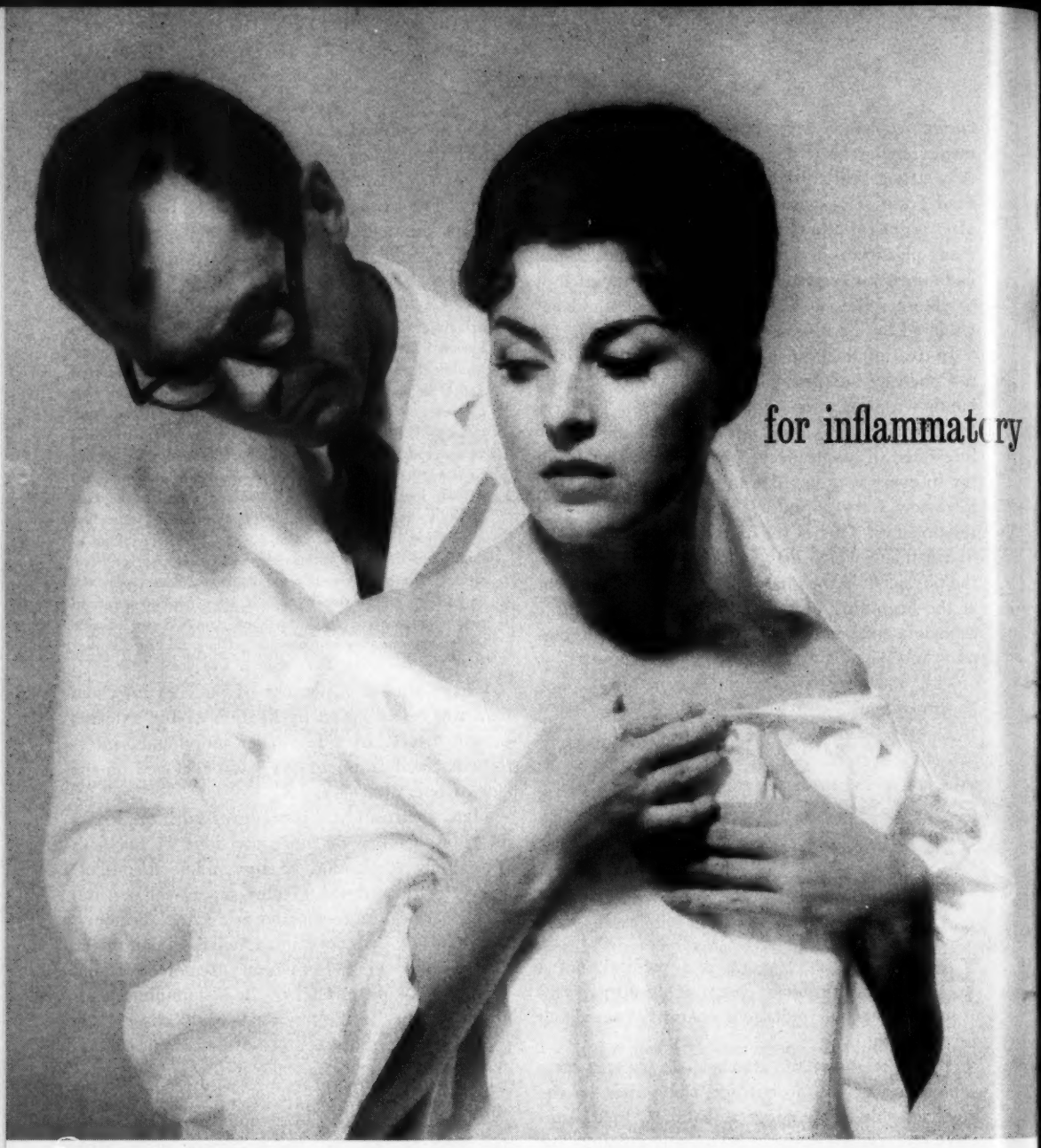
A physician, age 37, had had frequent and severe attacks of right histaminic cephalgia daily for five months before I first saw him in 1945. He responded to medical treatment at that time. Later, when the attacks recurred and after having repeatedly demonstrated to himself that compression of the right temporal artery gave momentary relief, he decided to have the right external carotid artery ligated. He had had daily attacks for six months prior to the operation. After the operation, he remained entirely free from attacks for two and a half years; then pulsations returned to the right temporal artery, indicating either that the external carotid artery had recanalized or that good collateral circulation had developed, or both. Attacks of right histaminic cephalgia again recurred, and he had the right external carotid artery ligated a second time and severed. The attacks of pain did not subside immediately as they had previously. They did cease a week after the operation, but recurred five years later.

I have studied a number of patients in whom pain was not relieved by ligation of the external carotid artery. In a few older individuals, intermittent claudication of the jaw developed on the side of operation (4).

Many neurosurgical procedures, such as alcohol injections of one or more divisions of the fifth cranial nerve, ligation of the middle meningeal artery, section of the greater superficial petrosal nerve, cervical or cervicothoracic sympathectomy, and, in a few instances, intracranial section of the fifth cranial nerve, have been attempted without obtaining complete relief of the histaminic cephalgia syndrome. If the physician could observe the patient during a severe attack of histaminic cephalgia, he would never mistake it for a major neuralgia.

Regardless of whatever operative procedures had been carried out, the histamine provocative test has been positive in this group of subjects. This test is of special interest in patients who have had intracranial section of the trigeminal nerve (case 9) or of the greater superficial petrosal nerve (case 12) or both.

Section of the greater superficial petrosal nerve (22)—I have studied eight patients with histaminic cephalgia who had had the greater superficial petrosal nerve sectioned. Six of these reported after the operative procedure that they no



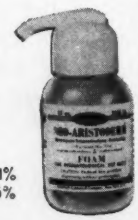
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Antibiotic Med. & Clin. Ther. 6:734 [Dec.] 1959.

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longer had tearing, plugging of the nostril, or rhinorrhea on the involved side. This is due to the fact that the greater superficial petrosal nerve carries secretory fibers to the ipsilateral lacrimal gland, and secretory and vasodilator fibers to the mucous membrane of the nasal cavity. It also carries vasodilator fibers to the ipsilateral cerebral hemisphere (29, 30). The pain pattern did not change, however. One patient reported that after the operation he seemed more sensitive to alcohol and even beer. He could no longer take a drink of whiskey or beer in the "free period" between series of attacks of histaminic cephalgia without provoking an attack, whereas before the operation he could always take a social drink without provoking an attack (case 12). Two patients had complete seventh nerve palsy after operation. The standard subcutaneous histamine provocative test which I performed was positive in four of the eight patients. If the test had been repeated, using a larger amount or even the same amount of histamine, I probably could have provoked an attack in all eight patients.

Treatment

IN THE TREATMENT of any type of headache, the physician's objective should be twofold: (1) to alleviate the pain during the attack and (2) to prevent further attacks.

Oxygen—One hundred per cent oxygen with a BLB mask is an extremely valuable therapeutic procedure in the management of histaminic cephalgia. If the use of oxygen is resorted to promptly at the onset of attacks of grade 1 or grade 2 pain, they can usually be aborted within a matter of minutes. Oxygen is a vasoconstricting agent which is not as powerful as dihydroergotamine or ergotamine tartrate.

In emergencies, when attacks were occurring every two or three hours or oftener, I have permitted patients to breathe 100 per cent oxygen for three-minute periods at hourly intervals throughout the waking hours. This procedure occasionally was carried out for three or four days.

Many of my patients have oxygen tanks at their bedside, so that when they are awakened at night they can use oxygen at once. A number of my patients have similar equipment in their office or place of business; a number carry oxygen tanks and BLB masks in their car while traveling. In my laboratory, oxygen tanks were always readily available; and during the years, innumerable attacks of grade 1 or grade 2 pain were thus aborted. We also treated other vasodilating headaches with oxygen.

In aborting induced attacks of histaminic cephalgia with histamine, we often used 100 per cent oxygen plus the intravenous administration of 1 cubic centimeter of dihydroergotamine methanesulfonate (D.H.E.-45), if the pain was of grade 3 or grade 4.

Cocainization of the sphenopalatine ganglion—On a number of occasions this procedure relieved the pain, but results were never uniform; a patient might obtain relief on one occasion but not on another.

Ergot preparations—In 1872, Silver (31) wrote a short article on use of ergot in headache. He stated, "I am not aware that it has been reported of use in the treatment of headache. It produces contraction of the muscular coat of the arteries . . . You can never certainly predict whether ergot will or will not do good in a certain case. I would have you try it, brethern, in every case and you will often be surprised with the result." His brief report from Ohio may be likened to a voice crying in the wilderness. It is the earliest report on ergot for headache that I have found.

In Day's book on headache (32), published in 1882, the statement is made: "Ergot is a remedy highly spoken of by some authorities, but I have not employed it with so many more remedies at hand . . . Dr. Brown explains its beneficial action by its influence in contracting the vessels of the brain, and administers the liquid extract of ergot . . ."

Thomson (33), in 1894, reported prompt relief of symptoms of migraine with the administration of ergot by rectum when vomiting prevented giving it orally. Robey (34), professor of medicine at Harvard, however, in his book on headache published in 1930, does not mention the use of ergot in the treatment of headache. Rothlin (35) reported that Stoll isolated ergotamine tartrate from ergot in 1918 and that it was first used in treatment for headache in 1926. The therapeutic effect of ergot, as had been suggested years earlier, depends on its ability to produce prolonged vasoconstriction by direct action on smooth muscle of blood vessels. Ergotamine tartrate, long in use, has become the drug of choice in treating the acute

vasodilating phase of migraine and other vasodilating head pains.

Dihydroergotamine methanesulfonate (D.H.E.-45) was prepared by Stoll and Hofmann in 1943, according to Rothlin (35). In 1945, Peters, Blumenthal, and I published our first evaluation of it in the treatment of headache. The incidence of toxic reactions was only a third that of ergotamine tartrate. In 1948, Ryan, Reynolds, and I (37) published the first controlled studies on the use of a combination of 1 milligram of ergotamine tartrate and 100 milligrams of caffeine (Cafergot,®* known then as E.C. 110). It is prepared in tablet form for oral or sublingual use and in the form of suppositories for rectal use. Wigraine® is a similar preparation of equal value when administered orally.

Successful use of ergot preparations depends on proper timing, method of administration, and dosage. Dihydroergotamine, for example, is the drug of choice for intravenous use, while ergotamine tartrate (Gynergen®) is best for intramuscular or subcutaneous use. Other ergot preparations can be given orally if nausea and vomiting do not prevent oral administration.

Rectal suppositories which contain appropriate amounts of ergotamine tartrate and caffeine frequently prevent nocturnal attacks if used at bedtime (figs. 5 and 9) and are more effective in this respect than ergotamine tartrate and caffeine given orally. A special study (1948 to 1949) on 78 of my patients with histaminic cephalgia showed excellent results in 90 per cent of 326 trials with suppositories containing ergotamine with caffeine (as Cafergot®) or with Bellafoline and pentobarbital added (as in Cafergot® P-B suppositories). The suppositories may be used for four to six consecutive nights or longer if necessary. A large quantity of suppositories containing various amounts of ergotamine tartrate and caffeine was used in my laboratory, beginning in 1948, before these preparations were placed on the market. I was more favorably impressed with the product known as E.C.B.P. 163, now marketed under the trade name of Cafergot® P-B, than with any other therapeutic agent which I used during this period.

While these preparations are extremely helpful if used wisely, their excessive use should be avoided. The toxic manifestations, for the most part, however, are not alarming. Intermittent claudication of the lower extremities developed in a number of patients who used ergot preparations excessively. The clinical picture mimicked that of occlusive arterial disease in the lower extremities. When the daily use of the drug was discontinued, all symptoms disappeared. The excess of this drug that some patients can take without being aware of toxic symptoms is amazing.

Histamine—Histamine, the most potent drug known to medical science, rightfully belongs in the atomic age. It was first prepared as a purely synthetic product in 1907 by Windaus and Vogt (38). In 1910 it was isolated from ergot by Barger and Dale (39). Its use is fraught with many pitfalls—too many for it to become a highly favored therapeutic agent within the immediate future.

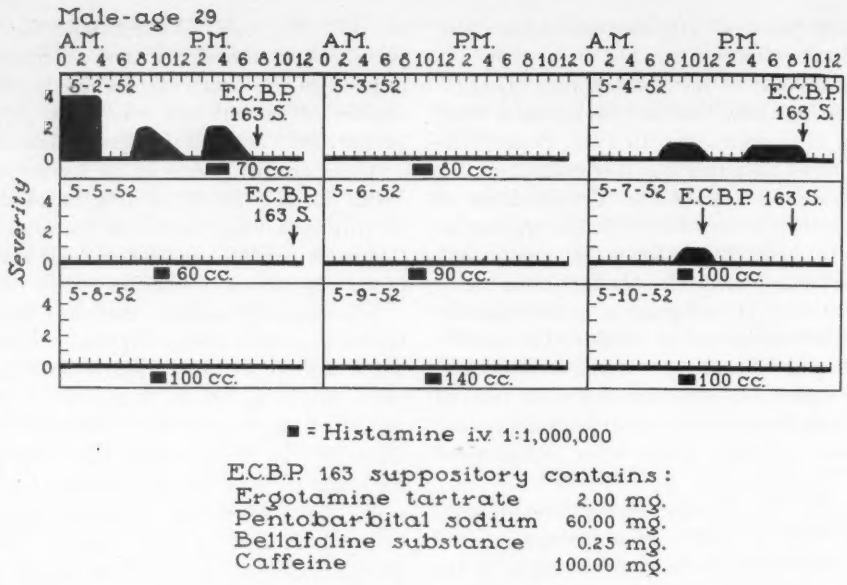
The histamine schedule must be flexible, not rigid. Its clinical use would be greatly simplified if histamine in the blood could be measured simply and accurately. Present methods are too time consuming and too expensive for routine clinical work.

In order to rationalize and fully appreciate the clinical use of histamine, it is necessary to know the pharmacologic and physiologic effects of this agent in humans. Hardly a tissue or an organ in the human body will not respond in some way to this powerful agent. Its participation in normal and disturbed physiologic processes has far greater significance than most physicians realize. It is not a cure-all, but it is an extremely useful drug if employed wisely.

Histamine desensitization—To prevent future attacks of histaminic cephalgia, histamine desensitization, in my opinion, is still the treatment of choice. Histamine therapy is neither simple nor commonplace. My procedure for the subcutaneous administration of histamine is as follows:

I use a 1 cubic centimeter ampule of 0.275 milligram per cubic centimeter of histamine diphosphate, which contains 0.1 milligram of histamine base. For the first dose, which is administered subcutaneously, I use 0.05 cubic centimeter from the ampule. Two injections are administered daily, about eight hours' apart. At each injection, the dose is increased by 0.05 cubic centimeter until 0.50 cubic centimeter is given. If, in some instances, this amount is not adequate, it is necessary to continue increasing the amount until 0.75 cubic centimeter

*Cafergot® (E.C.B.P. 163 and E.C.B. 115) used in my studies was supplied through the courtesy of Sandoz Pharmaceuticals.



■ = Histamine i.v. 1:1,000,000

E.C.B.P. 163 suppository contains:

Ergotamine tartrate	2.00 mg.
Pentobarbital sodium	60.00 mg.
Belladonna substance	0.25 mg.
Caffeine	100.00 mg.

Fig. 9

Number, severity, and duration of attacks. Patient had been having frequent and severe attacks for three weeks. Histamine was administered intravenously in a 1:1,000,000 solution for one to one and a half hours daily, for nine consecutive days. The blocking action of the E.C.B.P. 163 S. (Cafergot® P.B.) is evident. After using the suppository at 6 P.M. on May 2, 1952, the patient slept through the night without pain for the first time in three weeks. He was free from pain after the sixth day of treatment.

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or even 1 cubic centimeter is reached. Adequate dosage is determined by the patient's response.

If the symptoms are aggravated or seem to be precipitated by the injections, the patient may be undergoing sensitization rather than desensitization. In such a case, the subsequent dose is reduced by half, and the amount administered at each injection is again increased by increments of 0.05 cubic centimeter until a level just below that which precipitated the symptoms is reached.

The patient is taught to administer the injections to himself, whether the dose is 0.25 or 0.75 cubic centimeter. He is instructed to continue them twice daily for two or three weeks and once a day for an indefinite time thereafter. Some patients find it necessary to continue to use one or more injections daily in order to remain free of symptoms.

Many patients report a recurrence of symptoms coincidental with an infection of the upper part of the respiratory tract. The maintenance dose then is inadequate, and resuming the former desensitization schedule is often difficult because of the change in the patient's sensitivity. Many patients whose headaches recur report that they have tried to resume the desensitization schedule and to increase the dose to the former maintenance level without realizing that, with a recurrence of the attacks, their sensitivity to histamine is greater than it was during the previous episode.

It is usually easy to treat a patient with histaminic cephalgia when he is observed for the first time, provided he has not previously had histamine therapy. More than 90 per cent of my patients have responded to histamine desensitization, and the attacks, irrespective of their frequency and severity, have ceased in ten to twenty days. On the other hand, if the patient has had histamine therapy previously, and especially if the dose has been above the reaction level, attempts to repeat the procedure are increasingly difficult.

To treat a succeeding series of attacks of histaminic cephalgia, the dose is decreased consistently. Experience has shown that if the same dose employed in treating the first is used in treating the third series of attacks, the patient may be made worse instead of better.

For many patients, it has been necessary to give histamine intravenously in weak dilutions, ranging

from 1:1,000,000 to 1:20,000,000, by the drip method; and frequently these weak dilutions, when given at the rate of 30 drops per minute, will provoke an attack of histaminic cephalgia, usually within an hour (fig. 9 and table 5). This reaction provides a measuring stick, so to speak, to indicate, in a crude way, the patient's sensitivity to the drug. If, for example, an attack is provoked at the end of 60 minutes, administration by the drip method is carried out thereafter for 40 to 45 minutes. Many patients respond satisfactorily to this form of treatment. It can be carried out once or twice daily. To make a 1:10,000,000 solution of histamine, add 0.275 milligram of histamine diphosphate (0.1 milligram of histamine base) to 1,000 cubic centimeters of isotonic solution of sodium chloride.

It is difficult to outline a schedule which will fit any large group of patients. The schedule must be tailor-made to fit each patient.

Cortisone and ACTH—These agents may be used in conjunction with histamine in the management of patients with histaminic cephalgia, especially in treating succeeding series of attacks. That a patient's enhanced sensitivity to histamine can be altered by cortisone (compound E) was first demonstrated in 1941 after intramuscular injections of 20 and 40 milligrams of the hormone. I originally used Kendall's whole cortical extract for this purpose. Cortisone and corticotropin (ACTH) seem to alter the patient's reaction to histamine, or at least to "recondition" him so that he will again respond in a satisfactory manner to attempts at desensitizing. The reason for this has not been determined.

Only careful reports and observations of the patient's symptoms and response to injections in each 24 hours will give a clue to the schedule most satisfactory for each patient. Figure 7 indicates the method I used in one case. I originally thought that these agents would prove more useful than my subsequent clinical experience has confirmed.

Beta (2-pyridyl) ethylmethylamine hydrochloride (PT-9)—Walter, Hunt and Fosbinder (40) and Hunt and Fosbinder (41) first reported that the physiologic action of beta (2-pyridyl) ethylamine is similar to that of histamine (fall in cat's blood pressure and rise in rabbit's blood pressure). During the past eighteen years, I have worked with several of these pyridyl derivatives. Beta (2-pyridyl) ethylmethylamine hydrochloride (PT-9*), when taken orally in 1 milligram doses, seems to be a satisfactory substitute for subcutaneous injections of histamine for use in histamine desensitization in many subjects with histaminic cephalgia (fig. 4 and case 13). It has been an extremely difficult drug to evaluate accurately, so that my brief preliminary report may have to be revised later.

I have treated 175 patients with histaminic cephalgia with PT-9. My experience indicates that approximately 66 per cent have obtained good to excellent results. In many instances the results have been somewhat dramatic, only to have attacks recur later.

Illustrative Cases

CASE 5

Attacks completely controlled with histaminase (42) (fig. 1)—A man, age 56, registered at the Mayo Clinic on July 13, 1939. In 1935, daily attacks of right hemicrania had begun and persisted for fifteen months. These were worse in the summer months. He had a spontaneous remission which lasted until May, 1939. On admission, he had been having from one to three attacks each twenty-four hours for six weeks. Only six of the attacks had occurred during the day; the rest had occurred at night, usually after he had gone to sleep. With the day attacks, he could predict their onset a few minutes ahead of time, because his collar felt tight. Within ten minutes after this sensation, a toothache type of pain developed over the right side of his head. The right side of the head felt warmer, the right eye watered profusely and became bloodshot, the right nostril became plugged, and the pain became excruciating. The attacks lasted from five minutes to an hour. Cold compresses on the right side of the face and aspirin seemed to ease the pain a little. The right side of the neck, especially over the great vessels, felt tender after an attack.

The patient, having previously learned that drinking alcohol would precipitate an attack, had, therefore, refrained from its use. During the spontaneous remission, alcohol did not precipitate an attack, even if he consumed as many as five social drinks. He had no nausea, vomiting, or visual disturbances during these attacks. There was no history of migraine.

Routine general and neurologic examinations disclosed nothing of significance except Horner's syndrome on the right. The patient did not know how long this had been present. This was the first time I had observed Horner's syndrome associated with histaminic cephalgia. There was no disturbance of sweating over the right side of the face or the entire body. The blood pressure ranged from 118 to 155 systolic and 80 to 100 diastolic. Examination of the ocular fundi gave negative results; the right pupil

*PT-9 was supplied by Maltbie Chemical Co., Newark, N. J., and by Spencer Laboratories, Morristown, N. J.

Table 5
Histaminic Cephalgia: A Study of Histamine Tolerance

Age, yr. and sex of patient	Histamine by vein		Attack developed in minutes	Remarks
	Dilution	Drops per minute		
50 M	1:1,000,000	16–20	55	
45 M	1:1,000,000	16–20	50	
38 M	1:1,000,000	16–20	65	1st test
	1:2,000,000	12	55	2nd test
	1:4,000,000	16–20	20	3rd test
30 M	1:1,000,000	16–20	70	
60 M	1:1,000,000	20	70	
48 M (case 7)	1:7,500,000	16–20	45	
51 M	1:2,000,000	12	60	Same response in morning and afternoon of same day
54 M	1:10,000,000	24	40	1st test
	1:10,000,000	30	45	2nd test. Patient breathing 100 per cent oxygen had recovered from a spontaneous attack 25 min. previously. Repeated twice
49 M	1:15,000,000	30	50	
34 M	1:15,000,000	30	50	
42 M	1:15,000,000	25	60	
55 M	1:15,000,000	12	13	
53 M	1:15,000,000	25	85	
38 M	1:15,000,000	25	50	Same response 1 mo. later
33 M	1:15,000,000	25	20	1st test
	1:15,000,000	25	55	2nd test
55 M	1:15,000,000	72	100	
39 M	1:15,000,000	12	30	1st test
	1:15,000,000	25	13	2nd test
34 M	1:15,000,000	25	30	
57 M	1:1,000,000	24–30	40	1st test
	1:10,000,000	30	20	2nd test
	1:15,000,000	32	32	3rd test. Given 1 cc. of D.H.E.-45 just prior to administration
61 M	1:15,000,000	16–20	35	1st test
	1:15,000,000	16–20	30	2nd test

was smaller than the left. Routine laboratory studies, including urine, blood, serologic test for syphilis, and x-rays of the chest and head, gave negative results.

Special studies—The patient was given 1.2 milligrams* of histamine base in broken doses in approximately forty minutes. About twenty minutes after the last injection, a right hemicrania developed, which was in every way identical to the spontaneous attacks. As the attack came on, the first thing the patient did was to unbutton his collar. Shortly thereafter, the right eye began to water profusely, slight swelling developed in the soft tissue around the eye, beads of perspiration stood out on the right side of the forehead, and the right nostril became plugged. The excruciating pain which developed was confined to the right side of the head and neck. The face was flushed and was dark red. At first the pulse was accelerated from 100 to 136, but there were no changes in the blood pressure. The attack lasted about twenty minutes (fig. 1).

Nine histaminase tablets were administered daily, and by the end of the third day, attacks ceased. Each tablet was reputed to contain 5 units of histaminase, 1 unit being designated as the amount of histaminase required to inactivate 1 milligram of histamine when the two are incubated together in vitro for twenty-four hours at 37.5° C. Treatment with histaminase in this dose was continued for thirty-five consecutive days, during which time he had no attacks.

Control Study—Administration of histaminase was discontinued. The attacks of right histaminic cephalgia recurred sixteen days later, being as frequent and as severe as the earlier attacks. With resumption of histaminase in the same dosage, the attacks ceased in five or six days. The patient continued to take the same amount until January 8, 1940, when he began to reduce the number of tablets per day until March 4, at which time he discontinued their use. He reported on May 10, 1940, that he had been perfectly well and 100 per cent free from attacks since he had resumed the use of histaminase the previous summer. "Stopping that horrible pain is marvelous," he wrote.

CASE 6

Histamine desensitization: thirteen years' relief—A man 50 years old came under observation in November 1944. Seven weeks before coming for diagnosis and treatment, he had begun to suffer from a series of attacks of right-sided head pain, strongly suggestive of histaminic cephalgia. Most of the attacks occurred during sleep, and the pain was so severe that he would get out of bed. The right eye sometimes became red and teary. The right nostril invariably plugged and sometimes had a watery discharge. The pain was centralized in the right maxillary region.

The patient was treated with subcutaneous injections of histamine diphosphate, twice daily for five weeks, according to my standard method, and then every other day for an additional six weeks. Its use then was discontinued. The maximal dose was 0.4 cubic centimeter of our standard solution. At the end of five weeks he was entirely relieved and wrote thirteen years later that he had had no recurrence.

CASE 7

Failure of stellate ganglion block to abort induced attack of histaminic cephalgia—The patient, a local resident, was 48 years old. On December 13, 1954, a severe attack of right histaminic cephalgia developed. It was his first attack. The next day 100 milligrams of nicotinic acid was given subcutaneously three times at four-hour intervals, but he had attacks every two hours throughout the night. Cocainization of the right sphenopalatine region during an attack did not stop the pain. On December 15, when I saw him in consultation, he reported that on many occasions a drink of whiskey had provoked an attack.

I gave the patient histamine intravenously in a 1:7,500,000 solution by the drip method at the rate of 16 to 20 drops per minute. An attack of right histaminic cephalgia developed at the end of forty-five minutes. Thereafter, I treated him daily, in the same manner with the same strength of histamine solution, but for only forty minutes or less each day. By so doing, I avoided provoking additional attacks of histaminic cephalgia. The attacks lessened in frequency and severity and ceased completely in two weeks.

In September 1956, because of a recurrence, the possibility of cervical or cervicothoracic sympathectomy as a method of treatment was entertained. The question arose, can we provoke an attack of histaminic cephalgia with histamine and promptly abort it by stellate ganglion block? To partially answer the question, I gave the patient 0.35 milligram of histamine base subcutaneously on September 7 at 2 P.M.; no attack developed. The next day at 9:20 A.M., I gave him 0.4 milligram of histamine base subcutaneously. Ten minutes later a typical attack of grade 3 severity developed. At 9:58 A.M. 10 cubic centimeters of PAB_3, containing 0.5 per cent procaine hydrochloride, 2.5 per cent ammonium sulfate, and 3 per cent benzyl alcohol, was injected against the seventh cervical and first thoracic nerves on the right side; but the pain continued unaltered. At 10:05 A.M. 5 cubic centimeters and at 10:10 another 10 cubic centimeters of PAB_3 were injected into the same region. Complete Horner's syndrome promptly developed, but the pain remained unaltered.

On September 12, during an attack of pain, another consultant injected 12.5 milligrams of hydrocortisone around the right temporal artery; but this did not stop the pain or prevent future attacks. On the morning of November 27, 2 cubic centimeters of procaine was injected around the right temporal artery, in the hope of preventing future attacks; nevertheless, he had two attacks before 2 P.M. that same day. At 3 P.M. a consultant observed him in an attack and immediately injected 2 cubic centimeters of procaine around the prominent right temporal artery. The pain did not stop.

In September 1957, attacks recurred in a severe form. I saw him in consultation on September 19. He had recorded forty-two attacks during the previous four days. I gave him 40 units of ACTH-Z intramuscularly, at twenty-four-hour intervals for three successive days. He had eight attacks, though less severe, during this period, as compared with the twenty-four severe attacks during the pre-

*In 1939 0.35 mg. histamine base had not been established as the standard dose for the histamine provocative test.

vious three days. The attacks gradually faded away with additional ACTH-Z therapy. All attacks involved the right side of the head.

All of the special examinations and laboratory studies gave negative results in this patient. I do not have additional follow-up information; he was free from attacks the last time I saw him.

CASE 8

Positive provocative test and dramatic relief from stellate ganglion block—The patient, age 59, was given 0.35 milligram of histamine base subcutaneously at 9:38 A.M. in the operating room. He had no immediate reaction except a slight flushing of the face. Some residual soreness in the left temporal area had persisted since a severe attack of left histaminic cephalgia the previous night. The blood pressure was taken approximately every two minutes, and the surface temperature of both temporal areas was recorded at frequent intervals. The room temperature ranged from 88° to 90° F. The temperature of the skin of the face ranged from 95° to 97° F. We did not demonstrate any difference in the surface temperature of the two sides of the head, since to do so, the patient must be in an environmental temperature of 78° F. or less, with a relative humidity of approximately 40 per cent.

Thirty minutes after the injection of histamine, pain began in the left orbit and temporal region—and slowly increased, until 37 minutes after the injection of histamine, it became excruciating, causing him to writhe and twist. The patient said the attack was identical to the one of the previous night. The pain was entirely confined to the left side of the head.

The anesthesiologist blocked the left stellate ganglion, producing immediate and dramatic relief from pain. Left Horner's syndrome developed twenty minutes after the stellate block. The entire procedure covered a period of 45 minutes.

On August 18, 1956, left cervicothoracic sympathectomy was performed, from which the patient made an uneventful recovery. He wrote on March 2, 1957, that he had had no recurrence of his attacks of histaminic cephalgia.

I do not know why the stellate ganglion block gave dramatic relief in case 8 and failed to do so in case 7. In each instance, complete Horner's syndrome developed, indicating that the ganglion had been blocked. During this same period, I had a patient with left histaminic cephalgia under observation. He was suffering from two to three severe attacks each twenty-four hours, in spite of the fact that he had previously had cervicothoracic sympathectomy elsewhere.

The foregoing observations illustrate some of the difficulties which one encounters in the management of a patient with recurring attacks of histaminic cephalgia.

CASE 9

Numerous operative procedures including intracranial section of the left trigeminal nerve—A man, age 43, came to the clinic on July 30, 1953. He had enjoyed excellent health until his thirty-third year, when, with no apparent reason, a burning pain developed inside the left nostril and spread to the left orbit and left temple. The pain persisted for thirty minutes and was associated with pronounced redness and tearing of the left eye and plugging of the left nostril. The severity of the pain caused him to throw himself on the floor and bang his head. Occasionally he felt nauseated, but had no vomiting or visual disturbances. These attacks at first occurred once a month; however, by the end of the third month, he had them both night and day, but more frequently during the night. Remissions did not occur.

Beginning three years after the onset, the following operative procedures were carried out: 1. All of the upper teeth were extracted. 2. Two months later a long incision was made along the course of the left common carotid artery; apparently a "periarterial sympathectomy" had been carried out. 3. Two years later an incision was made through the left eyebrow, and "nerve fibers were evulsed." 4. One week later the left trigeminal nerve was sectioned intracranially. 5. Finally, a month after the last operation, the left occipital area was explored; but no brain tumor was found. None of these procedures altered the frequency or severity of his attacks of pain.

There were no significant findings on the general or neurologic examinations, except for those secondary to the various surgical procedures. Vision was 6/6 and 14/21. The patient did not have Horner's syndrome, but it developed on the left side during an attack induced by histamine. The laboratory reports gave negative results, except for the roentgenogram of the head, which showed defects due to craniotomy in the left temporal and left occipital areas.

From 1942 until I saw him in August 1953, he had one to six attacks every twenty-four hours. The distribution of the pain remained the same as before the operative procedures, but the character of the pain had seemed to change. He referred to it as a "sickening, dull pain" rather than a burning pain.

Histamine provocative test—On August 4, 1953, at 2:35 P.M. I gave the patient 0.35 milligram of histamine base subcutaneously without his being aware of the fact that I was endeavoring to provoke an attack. I conversed with him during the entire procedure, but no mention was made of a provocative test. Immediately after the injection of histamine, he had "a funny, faint feeling" in his head, and a minute later he reported a slight frontal distress. Three minutes later he complained of a throbbing sensation in the right side of his head. These subjective sensations represented the physiologic effects of the drug. They gradually ceased, and for ten minutes he felt normal. Twenty-six minutes after the injection of histamine, one of his typical attacks developed, involving the left cheek, the left orbit, and the left temporal areas.

The conjunctiva of the right eye appeared more congested than that of the left, and tearing of the right eye was noted. The palpebral fissure on the left was narrowed 50 per cent (left Horner's syndrome). At the height of the pain, left rhinorrhea and plugging of the left nostril

occurred. Sweating was present over the forehead, being more evident on the right side. Sweating seemed uniform over the upper lip. He had almost complete loss of sensation over the distribution of the second and third divisions of the left trigeminal nerve and anesthesia, minus 2 to minus 3, above the left eye. The left corneal reflex was minus 3.

I observed the patient during the induced attack for fifteen minutes. The pain was steady; he had no nausea or vomiting; his eyes were insensitive to light. Injection of 1 cubic centimeter of D.H.E.-45 gave complete relief in less than eight minutes.

From the time the patient had registered at the clinic, on July 30, 1953, he had had fifteen spontaneous attacks of left head pain. Except for two relatively mild attacks, all were severe. While chatting with him immediately after the provocative test, I asked, "How did you get along last night?" He replied that about an hour after going to bed he was awakened by a severe attack which lasted from 12:00 to 12:30 A.M. Another severe attack occurred from 2:00 to 2:30 A.M., a third from 5:00 to 5:20 A.M., and a fourth from 7:00 to 8:00 A.M.

Later attacks—After the positive histamine provocative test he had no attacks of left head pain during the night and for approximately twenty-nine hours thereafter. One recurred at 10:30 P.M. and lasted one hour. Additional attacks occurred at 12:30 A.M. (grade 4, which lasted for an hour), at 3:00 A.M. (grade 1, lasting for fifteen minutes), at 4:30 A.M. (grade 2, which lasted for twenty-five minutes), and at 6:30 A.M. (grade 3, which lasted for an hour).

Subcutaneous histamine therapy was instituted immediately after the provocative test, but this patient proved to be extremely difficult to treat. He suffered 106 attacks of histaminic cephalgia from the time treatment was instituted until cessation of attacks six days before his dismissal on September 18, 1953.

To overcome some of the difficulties encountered in regulating the subcutaneous injections of histamine (the maximal amount for a given injection was 0.7 cubic centimeter of the standard solution), I gave the patient 30 milligrams of corticotropin (Acthar®) on September 17. The next day he was given histamine intravenously in a 1:7,500,000 dilution at the rate of 20 drops per minute from 9:00 to 10:00 A.M. and again from 3:15 to 4:15 P.M. This procedure was repeated on two additional days. Subcutaneous histamine therapy was maintained throughout this period. The patient was advised to continue subcutaneous histamine therapy, 0.45 cubic centimeter twice daily, after returning home and to reduce the therapy to once daily after one month.

I have not heard from this patient since his dismissal. The clinical course of this patient illustrates that grade 3 or 4 attacks of histaminic cephalgia are much easier to treat than attacks of grade 1 or 2. I have made this observation many times.

CASE 10

Histaminic cephalgia and palindromic arthritis—A physician, age 40, had had histaminic cephalgia and palindromic arthritis since 1927. When he first came to the clinic in 1945, he was having attacks of histaminic cephalgia twice daily and episodes of palindromic arthritis of three to four days' duration, occasionally for as long as two weeks.

Subcutaneous histamine desensitization was instituted, and on dismissal two weeks later, he was relieved of both conditions.

About five years later he returned, saying that he was no longer able to control his attacks of histaminic cephalgia by means of subcutaneous injections of histamine. At 10:55 A.M., when I saw him, I gave him 3 cubic centimeters of Kendall's cortical extract intravenously, one hour later 6 cubic centimeters then 10 cubic centimeters every hour for four hours. The total dosage was 49 cubic centimeters. He seemed to feel better at once. Subcutaneous histamine therapy was reinstituted, and he was told to take 0.2 cubic centimeter twice a day and not to increase the dose. His attacks ceased within three or four days.

CASE 11

Histaminic cephalgia and rheumatoid arthritis treated with cortisone—A man, age 50, was having nightly attacks of histaminic cephalgia at the time cortisone therapy for rheumatoid arthritis was instituted in July 1950 by a physician in his home locality. He received 300 milligrams the first day, 200 milligrams the second day, 100 milligrams for five successive days, and 75 milligrams daily thereafter.

The headaches subsided for a month, then recurred with the same frequency and severity and continued without change throughout the thirteen months of cortisone treatment.

He explained, "Before I took the cortisone, I was so stiff and sore I could not walk; but when the head pain hit me, it made me sit up in bed. Since taking cortisone, my head pains are just as bad as ever; but when the attack comes on, I'm now able to get out of bed and pace the floor."

CASE 12

Cessation of tearing of the eye and rhinorrhea on section of the greater superficial petrosal nerve—A 41-year-old man with typical attacks of right histaminic cephalgia had repeatedly perceived that a glass of beer or whiskey would provoke an attack during a given series of attacks, but not during periods of remission. After having the right greater superficial petrosal nerve cut, in an attempt to eradicate the attacks, he noted that the drinking of beer or stronger alcoholic beverage would provoke an attack during a remissive period as well as during a series. Although the operation did not alter the frequency or severity of the attacks, it did result in the tearing of the right eye and the plugging and rhinorrhea of the right nostril. The pain seemed less severe in the right orbit, but the over-all pain pattern was not altered. He also seemed more sensitive to histamine.

I employed a 1:15,000,000 solution of histamine, administered intravenously, whereupon his attacks promptly ceased.

CASE 13

Migraine, hypertensive headache and histaminic cephalgia—A female patient, age 64, who clearly distinguished

between these three types of headache, was prompted by the histaminic cephalgia attacks to come to the clinic. She had had classic migraine at infrequent intervals since early childhood.

The hypertensive headaches were mild, involved the occipital region, came on in the early morning, and were relieved by drinking coffee. Blood pressure was 178/96, 180/96, and 130/90.

The histaminic cephalgia had developed two years prior to the patient's admission in February 1957. She had been averaging two severe attacks every twenty-four hours for three or four months. "They come on when I'm asleep at night, 1:00 to 3:00 A.M., and when I take a nap in the afternoon. When they hit me, I can't stay in bed. The onset seems sudden, and they stop in a like manner. The left eye becomes red and waters, and the left nostril plugs. It is a steady, burning pain. It never lets up (or so it seems), but when it does, it is sudden—and it's all over. I gag every time, but no food comes up."

Her eyes were not sensitive to light. Treatment with subcutaneous injections of histamine had stopped attacks after a week. Although treatment was continued, the attacks recurred. She had received no histamine for a month before admission.

I gave her 1 milligram of PT-9 by mouth three times daily. The attacks of left histaminic cephalgia ceased within ten days. She was instructed to continue to take 1 milligram of PT-9 daily. She wrote eleven months later that the drug had given good results.

Chance Observations

CHANCE OBSERVATIONS have often played an important part in medical discoveries, but they favor only the mind which has been previously prepared to receive them.

An amazing number of studies and thought-provoking observations were made in the 1,402 patients with histaminic cephalgia who were under surveillance in my laboratory for varying periods. For example, a 50-year-old man had 386 attacks of right histaminic cephalgia while under observation for two months. Of the 386 attacks, 91 were of grade 4 severity; 48 were grade 3; 116, grade 2; and 131, grade 1.

Only a few of these observations can be alluded to in this paper.

Closing Thoughts

THE PRACTICE OF MEDICINE lags behind the science of medicine. Nowhere is this fact better illustrated than in the use of histamine as a therapeutic agent. The steps from the original discovery of a therapeutic agent to its practical clinical application often are long and complex. The art of medicine and the science of medicine must be happily blended at appropriate levels for the physician to achieve complete success in the management of histaminic cephalgia.

There is a great need for "headache clinics," comparable to metabolic clinics and rheumatic clinics, where adequate specialization in the treatment and study of headache and head and face pain can be carried on and where more serious attempts can be made to investigate the fundamental aspects of these problems. It is a fruitful field for clinical investigation. The patients are numerous; the workers are few. Control of pain is still a challenge to modern medicine.

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REFERENCES

1. Ekbom, K. A.: Acta psychiat. et neurol. Suppl. 46, 1947, pp. 105-113.
2. Horton, B. T.: J.A.M.A. **116**:377-383 (Feb. 1) 1941.
3. Horton, B. T.: J.A.M.A. **122**:59 (May 1) 1943.
4. Horton, B. T.: Tr. Am. Acad. Ophth. **49**:23-33 (Sept-Oct.) 1944.
5. Horton, B. T.: M. Clin. North America, July, 1949, pp. 973-1005.
6. Horton, B. T.: Postgrad. Med. **9**:1-10; 88-100 (Jan.) 1951.
7. Horton, B. T.: **72**:92-98 (Feb.) 1952.
8. Horton, B. T.: Bull. Tufts-New England M. Center. **1**:143-156, 1955.
9. Horton, B. T.: Proc. Staff Meet., Mayo Clinic. **31**:325-333 (May 30) 1956.
10. Horton, B. T.: J.A.M.A. **160**:468-469 (Feb. 11) 1956.
11. Horton, B. T.: Angiology **10**:43-56 (Feb.) 1959.
12. Horton, B. T., MacLean, A. R., and Craig, W. McK.: Proc. Staff Meet., Mayo Clin. **14**:257-260 (Apr. 26) 1939.
13. Leyton, N.: Migraine and Periodic Headache: A Modern Approach to Successful Treatment. Ed. 2, London, William Heinemann Medical Books, Ltd., 1954.
14. Marsiaj, N.: Sindrome de Horton. In: Clínica Médica: Lecciones de patologia y de clínica. Buenos Aires, El Ateneo, 1948, pp. 429-471.
15. Peters, G. A.: Migraine: Proc. Staff Meet., Mayo Clin. **28**:673-686 (Dec. 2) 1953.
16. Ryan, R. E.: Headache: Diagnosis and Treatment. St. Louis, C. V. Mosby Company, 1954.
17. Robinson, B. W.: Medicine. **37**:161-180 (May) 1958.
18. White, J. C., and Sweet, W. H.: Cephalic Pain, Transmission Pathways Uncertain. In: Pain: Its Mechanisms and Neurosurgical Control. Springfield, Illinois, Charles C. Thomas, 1955, p. 494.
19. Boies, L. R.: Ann. Otol., Rhin. & Laryng. **59**:507-517 (June) 1950.
20. Sluder, G.: New York J. Med. **87**:989-990 (May 23) 1908.
21. Vail, H. H.: Ann. Otol., Rhin. & Laryng. **41**:837-856 (Sept.) 1932.
22. Gardner, W. J., Stowell, A., and Dutlinger, R.: J. Neurosurg. **4**:105-114 (Mar.) 1947.

23. McElin, T. W., and Horton, B. T.: Ann. Int. Med. **27**:749-768 (Nov.) 1947.
24. Horton, B. T., Magath, T. B., and Brown, G. E.: Proc. Staff Meet., Mayo Clin. **7**:700-701 (Dec. 7) 1932.
25. Horton, B. T., and Magath, T. B.: Proc. Staff Meet., Mayo Clin. **12**:548-553 (Sept. 1) 1937.
26. Kleckner, M. S., Jr., and Horton, B. T.: Gastroenterology **13**:141-143 (Aug.) 1949.
27. Huković, S., Spuzić, I., and Stern, P.: Arch. internat. pharmacodyn. **109**:285-293 (Feb.) 1957. (Abstract. J.A.M.A., June 8, 1957, p. 709.)
28. Browne, H. C.: Skin Reactions as an Index to Desensitization to Histamine. Thesis, Graduate School, University of Minnesota, 1940.
29. Chorobski, J., and Penfield, W.: Arch. Neurol. & Phychiat. **28**:1257-1289 (Dec.) 1932.
30. Cobb, S., and Finesinger, J. E.: Arch. Neurol. & Psychiat. **28**:1243-1256 (Dec.) 1932.
31. Silver, D. R.: M.&S. Reporter **2**:361 (Oct. 19) 1872.
32. Day, W. H.: Headaches: Their Nature, Causes and Treatment. Philadelphia, Blakiston Company, 1882.
33. Thomson, W. H.: J. Nerv. & Ment. Dis. **21**:124-125 (Feb.) 1894.
34. Robey, W. H.: Headache. Philadelphia, J. B. Lippincott Company, 1930.
35. Rothlin, E.: Internat. Arch. Allergy. **7**:205-209, 1955.
36. Horton, B. T., Peters, G. A., and Blumenthal, L. S.: Proc. Staff Meet., Mayo Clin. **20**:241-248 (July 11) 1945.
37. Horton, B. T., Ryan, R., and Reynolds, J. L.: Proc. Staff Meet., Mayo Clin. **23**:105-108 (Mar. 3) 1948.
38. Windaus, A., and Vogt, W.: Ber. deutsch. chem. Gesellsch. **40**(pt. 3) :3691-3695, 1907.
39. Barger, G., and Dale, H. H.: J. Physiol. **40**:38-40, 1910.
40. Walter, L. A., Hunt, W. H., and Fosbinder, R. J.: J. Am. Chem. Soc. **63**:2771-2773 (Oct.) 1941.
41. Hunt, W. H., and Fosbinder, R. J.: J. Pharmacol. & Exper. Therap. **75**:299-307 (July) 1942.
42. Roth, Grace M., and Horton, B. T.: Bull. New York Acad. Med. **16**(series 2) :570-584 (Sept.) 1940.

VIRGINIA BEYER MEMORIAL LECTURE

The Department of Psychological Services, Springfield State Hospital, announces that the Virginia Beyer Memorial Lecturer for 1961 will be Florence Halpern, Ph.D. Her topic will be "The Interpretation of Children's Rorschach." The lecture will take place April 21 at 10:00 A.M. in the Auditorium, Geriatrics Building. For further information write to Michael H. P. Finn, M.D., chief of psychological services, Springfield State Hospital, Sykesville, Maryland.

CALENDAR OF EVENTS

► Thursday, April 20 ◄

OPHTHALMOLOGICAL SECTION, B.C.M.S.
Sheraton Belvedere Hotel
6:00 Cocktails 7:00 Dinner
8:00 Scientific Session: "Unilateral Exophthalmos," Richard D. Richards, M.D.

► Tuesday, April 25 ◄

ANESTHESIA STUDY COMMITTEE
8:00 P.M., 1211 Cathedral Street

COMMITTEE FOR THE STUDY OF PELVIC CANCER
9:30 P.M. North Charles General Hospital

► Wednesday, April 26-Friday, April 28 ◄

MEDICAL AND CHIRURGICAL FACULTY OF MARYLAND
Annual Meeting
The Alcazar

► Wednesday, April 26 ◄

BALTIMORE CITY DENTAL SOCIETY
Assembly Room, Sheraton Belvedere Hotel

► Saturday, April 29 ◄

MEDICINE 1961
4:30-5:00 P.M. WMAR-TV
Panel Discussion on "Obesity"

► Saturday, May 6 ◄

MEDICINE 1961
4:30-5:00 P.M. WMAR-TV
"Your Hospital—A Community Partnership"

► Sunday, May 7-Wednesday, May 10 ◄

MARYLAND STATE DENTAL ASSOCIATION
Annual Meeting
Lord Baltimore Hotel

► Monday, May 8 ◄

SACRED HEART HOSPITAL MEDICAL STAFF
11:30 A.M.
School of Nursing,
Bellevue Street, Cumberland

► Tuesday, May 9 ◄

MARYLAND SOCIETY ON ALCOHOLISM
Officers and Executive Committee
8:00 P.M. Council of Social Agencies,
22 Light Street

COMMITTEE FOR THE STUDY OF PELVIC CANCER
4:30 P.M. Madison House, North East, Md.
Meeting with the Cecil County Medical Society

► Wednesday, May 10 ◄

MARYLAND TRUDEAU SOCIETY
Second Annual Meeting
Emerson Hotel
Victor A. McKusick, M.D., will discuss his recent experiences in Korea.

MARYLAND SOCIETY FOR MENTALLY RETARDED CHILDREN
GREATER BALTIMORE CHAPTER
8:15 P.M., 2525 Kirk Avenue



• *clinical pathological conference from Provident Hospital, Baltimore, Maryland.*

Hsiang Len Tseng, M.D.

A 50-year-old Negro male was admitted to the Provident Hospital on September 15, 1958. He had had a fever of undetermined origin and generalized muscle aching for about two months. His personal physician heard rales throughout the chest and treated the patient with penicillin and streptomycin. His temperature returned to normal limits on this therapy. Three weeks before admission to the hospital, he became aware of frequency of urination and defecation, as well as nocturia. One week before admission, he complained of pain in his left great toe, which was followed by fever which lasted for two days.

Significant events of his past history include repair of an inguinal hernia and a suprapubic operation for "stricture of urethra." The pain in the left great toe had been evaluated at another hospital; x-ray examination revealed no abnormalties in the bone.

Physical examination admission revealed that the patient was alert and ambulatory and that he walked with a limp. Blood pressure was 130/92; pulse rate was 120 per minute; respirations were 50 per minute; and temperature was 103.6.

Positive physical findings included a few palpable cervical lymph nodes in the neck and fine crackling and crepitant rales bilaterally. The heart was not enlarged, nor were murmurs or thrills present at this time. Abdominal examination was negative, and the spleen, liver, and kidneys were not palpable. The posterior tibia and pedis dorsalis pulsations were strong and equal on both sides. The left great toe was warm, red, and tender. Pain was elicited with pressure and on passive movement of the left first metatarsal-phalangeal joint. Lesions suggestive of dermatophytosis were present in both feet, and there was a slightly indurated edema in both lower legs.

The initial laboratory findings showed the hemoglobin to be 8.7 grams, hematocrit 30 volumes per cent, RBC 3.01 mil., WBC 20,600 with 75 per cent neutrophiles and 25 per cent lymphocytes. The urine had a specific gravity of 1.011, 3 plus protein, negative sugar, moderate amounts of WBC and an occasional RBC, and one to two granular casts per high power field. The blood chemistry showed the glucose to be 60.5 milligrams per 100 milliliters; NPN 28.2 milligrams per 100 milliliters; CO_2 25.6 milliequivalents per liter; chloride 91.6 milliequivalents per liter; potassium 3.56 milliequivalents per liter; sodium 131.2 milliequivalents per liter; phosphorus 3.3 milligrams per 100 milliliters; albumin 2.2 grams, and globulin 4.7 grams. The van den Bergh was negative, and the blood cholesterol was 140 milligrams with 60 milligrams per 100 milliliters cholesterol esters. The alkaline phosphatase was 210 units; prothrombin time was 43 per cent of normal. The SGOT was 20 units, and the SGPT was 40 units. The agglutination study showed that the serum was negative for typhoid, paratyphoid, Proteus, and brucellosis. The heterophile agglutination was positive up to the 1/28 dilution. The nose culture showed non-hemolytic streptococci. The blood culture on two occasions was positive for non-hemolytic Staphylococcus aureus and one occasion was positive for non-hemolytic streptococcus. Serologic examination was negative. Blood was type O and was Rh negative.

The initial x-ray study on September 15, 1958, revealed a linear density at the base of the left lung posteriorly, and the impression was segmental atelectasis.

The patient had a spiking temperature up to 104-105 with an elevated base throughout his hospitalization. On the first three days, in addition to the spiking temperature, tachypnea, tachycardia, and general weakness were the main features of the disease. On the fourth day he became delirious and paranoic, with ideas that someone was trying to kill him. His temperature at that time was 104°. With supportive therapy, the temperature and hallucinations gradually subsided. On the

sixth day, abdominal distention was pronounced, and the patient passed large amounts of gas. The distended abdomen added to his difficulty in breathing.

X-ray examination at this time showed the small and large bowels to be distended with gas, suggesting paralytic ileus. The repeat chest film showed increased pulmonary congestion, rounded densities in both right and left lung fields, and a widening of the superior mediastinal shadow. The rales in the basilar portions of both lungs persisted during these days. Heart sounds remained good in spite of a split first sound at the apex. The pain in the left great toe was still present with passive motion, and the x-ray report noted a small defect on the medial aspect of the first metatarsal bone, compatible with early gout.

During this period, the positive laboratory findings included persistent proteinuria, as well as red blood cells and leukocytes in the urine. Leukocytosis was present with marked shift to the left and anemia of a normocytic normochromatic type. The calcium levels remained low, varying from 6.6 to 8.44 milligrams per 100 milliliters, and the phosphorus ranging from 3.0 to 4.2 milligrams per 100 milliliters. The reversed A/G ratio persisted until late in his illness, when the albumin was found to be 4.8 grams and globulin 3.7 grams. The uric acid was 5.6 milligrams per 100 milliliters. The electrocardiogram showed tachycardia, sinus in origin, with no evidence of hypocalcemia or hyperkalemia.

The patient was treated with streptomycin and penicillin. On the eleventh day of hospitalization Cathomycin® and Aristocort® were used. Later Achromycin® was also given. After the introduction of Cathomycin® and Aristocort,® the temperature fell to 99 on the sixteenth and seventeenth days after admission. On the seventeenth day, however, the fever developed a septic character, varying from 96.6 to 103.6, until the twenty-fourth day, when death ensued.

Clinical diagnosis was, bronchopneumonia, septic, probably staphylococcal

On autopsy, the heart was enlarged, weighing 500 grams. The tricuspid valve measured 13 centimeters in circumference. Along the ring of the ventricular surface of the anterior leaflet were large yellowish-tan friable vegetations (fig. 1), which measured 4.5 by 2.2 by 1.5 millimeters. There was no calcification or other deformity of



Fig. 1

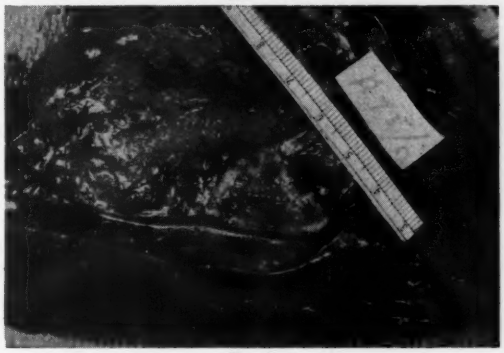


Fig. 2

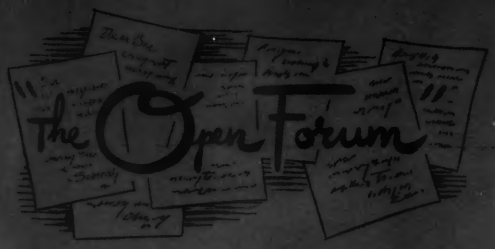
the tricuspid valve. Culture made from the vegetations grew nonhemolytic Staphylococcus aureus. No evidence of healed valvulitis was found on any of the four valves.

The right and left lungs weighed 460 and 530 grams, respectively. Both lungs showed many large, fairly defined, wedge-shaped, yellowish areas on the pleura and on the sectioned surfaces. These averaged 3 centimeters in diameter. Many of the pulmonary arteries were entirely or partially occluded by the emboli (fig. 2).

Final anatomical diagnosis was:

1. Acute bacterial endocarditis of tricuspid valve, non-hemolytic, Staphylococcus aureus
2. Multiple septic embolism and infarction of both lungs
3. Hemothorax: slight
4. Chronic lymphadenitis of hilar lymph nodes
5. Chronic perisplenitis and splenitis
6. Embolic focal glomerulitis
7. Acute ulcerative esophagitis.

1514 Division Street
Baltimore 17, Maryland



We invite you to share your views, to compliment or to criticize, to support or to refute ideas and issues of concern to Maryland physicians. Address your letters to The Open Forum, Maryland State Medical Journal, 1211 Cathedral Street, Baltimore 1, Maryland. Please keep your letters brief and to the point. Your name and address must be included, but we will withhold your name upon request. Errors in grammar, spelling, and punctuation will be corrected unless you specify that the letter be published as is. Opinions expressed in The Open Forum are not necessarily those of the editor of the Maryland State Medical Journal or of the Medical and Chirurgical Faculty

Chemical versus trade names

Your January editorial in the Maryland State Medical Journal was obviously biased. I feel strongly that the other side of the picture must be presented.

It has been my experience that enormous savings are available to the patient when the chemical name is used instead of the trade name, without significant effect on the therapeutic regimen. Medical costs are high. Savings are particularly important to patients who require expensive drugs for long periods.

It would have been more prudent for the editor to have obtained information regarding costs and content of generic equivalent drugs from an unbiased source. Information is available from the Food and Drug Administration, also from an independent group of university physicians who publish a non-profit periodical, "The Medical Letter on Drugs and Therapeutics." The latter group is in the process of evaluating generically equivalent drugs. They found that the variation in content in forty-two different manufacturers' samples of prednisone were "borderline and of no clinical significance." The cost to the druggist of prednisone varies from $1.70 to $17.90 per hundred. They examined twenty-seven manufacturer's samples of secobarbitol, and found in fifteen hundred individually weighed capsules, only thirty varied by more than 25% from the average weight.

In a recent discussion with a physician in the Food and Drug Administration, I was told that they rarely found significant deviations from the labeled content. It had been their experience that some of the large drug manufacturers were as often found at fault as the smaller ones. In a research project, these differences might be significant; but in the general practice of medicine, considering all the variations in patient attitude as well as physical make up and disease status, it certainly is not significant if their tablet has 4.5 mgs. or 5.5 mgs. of prednisone. (If the patient is taking a number of pills, the superfluous would probably balance the deficiency). However, to a considerable number of patients it is extremely important to them if they pay $5.00 per hundred or $27.00 per hundred tablets of prednisone. It is not uncommon for patients to take oral penicillin as a prophylactic measure against streptococcal infections for years. Several of the local pharmacists carry the same tablet as recommended by the American Heart Association, that sells for $16.00 per hundred under one label, generically prescribed can be obtained for $4.00 per hundred.

The question of research in relation to drug price, I believe, is overrated and certainly is used in many instances where it does not apply, such as in simply making a penicillin tablet where no research is involved, or the prednisone tablet for which four large drug companies charge $17.90 per hundred although apparently only one did the research. Twelve other concerns sell the same product for under three dollars per hundred.

Let us consider the whole patient; not everyone can or wants to drive a Cadillac.

—Irving L. Ochs, M.D.
51 Southgate Avenue
Annapolis, Maryland

ALLEGANY-GARRETT COUNTY MEDICAL SOCIETY

LESLIE E. DAUGHERTY, M.D.

Journal Representative

DR. MOCK DISCUSSES CLINICAL USES OF RADIOACTIVE ISOTOPES



IN SUMMARIZING his remarks at the conclusion of an animated motion picture on Radioactive Isotopes, **George F. Mock, M.D.**, reported the following information:

In diagnosis, iodine 131 determines thyroid activity, while vitamin B_{12} cobalt 60 differentiates pernicious anemia.

In therapy, radioactive iodine is used for hyperthyroidism, metastatic carcinoma of the thyroid, and in cardiac disease.

Radioactive phosphorus is used in polycythemia vera, chronic leukemia, and diffuse metastatic carcinoma to the bones.

Colloidal radioactive gold is used prophylactically in ovarian carcinoma and may be used palliatively in recurrent malignant ascites and pleural effusion.

Dr. Mock's discussion on the clinical uses of radioactive isotopes was presented at the Medical Surgical Chest Disease Conference, held at Cumberland's Memorial Hospital.

Pessimism is only cowardice reduced to a system.

—Plutarch

PHYSICIAN SPEAKERS

At a recent meeting of the Allegany-Garrett County medical assistants, **Mikio Kato, M.D.**, of Frostburg, accompanied his talk with slides of Tangier Island, his former home.

George M. Simons, M.D., of Cumberland, spoke at a meeting of the Maryland Association of Medical Assistants, which was held in Baltimore. His topic was "What a General Practitioner Expects of his Medical Assistant."

At Parent-Teacher Association meetings in Cumberland schools, **Benedict Skitarelic, M.D.**, and **Leo H. Ley, Jr., M.D.**, conducted a question and answer period after the showing of two films on cancer. The films were entitled "Never Alone" and "Time and Two Women." **Gina Glick, M.D.**, spoke on the Tri-State Poison Control Center, which has been established at Sacred Heart Hospital.

Leland Ransom, M.D., in a talk on civil defense before the Cumberland Mothers Club, stressed the necessity for individual fallout shelters. He also gave a demonstration of radioactive materials and of emergency radio communications. Dr. Ransom is president of the Amateur Radio Club of Allegany County.

Walter Himmler, M.D., of Cumberland, was guest speaker at a meeting of District I., Maryland Nurse's Association. His topic was "Kidney Functioning Tests."

Anger turns the mind out of doors and blocks the entrance.

—Plutarch

PERSONALS

Carlton Brinsfield, M.D., president of the staff of Memorial Hospital, Cumberland, officiated at the crowning of a queen. The coronation took place at the annual valentine dance sponsored by the students at Memorial Hospital School of Nursing.

The Legion of Honor Degree was presented recently to **Clay Durrett, M.D.,** of Cumberland. This is the highest honor that can be conferred by the Grand Council of Demolay.

BIRTHS

Dr. and Mrs. George F. Mock announce the birth of a son on February 25 at Cumberland's Memorial Hospital.

BALTIMORE COUNTY MEDICAL ASSOCIATION

LOUIS DALMAU, M.D.

Journal Representative

A membership directory of the Baltimore County Medical Association will be published this year. Present membership is 250. The Association will initiate a recruitment campaign aimed at qualified nonmember physicians who live or practice in Baltimore County.

The minimum attendance requirement for continuous active membership is two meetings a year. The requirement will be enforced this year.

George C. Medairy, M.D., recently retired director of Rosewood State Training School, will be given a testimonial plaque in recognition of his services to the mentally retarded. He has been a member of our Association for many years.

Robert Hening, M.D., who has had an exemplary membership and medical career in Baltimore County, has been elected to emeritus membership by the Faculty's House of Delegates.

The Baltimore County Medical Association contributed $25.00 to the Children's Aid Society.

J. Morris Reese, M.D., who, as chairman of the Advisory Board of Health, officially and capably represented the medical profession in Baltimore County, presented a report covering the past year and a half. Since September 1959, the Board has strictly followed the recommendations of the School of Hygiene and Public Health, headed by **Ernest Stebbins, M.D.** The creation of the Advisory Board of Health to work with the Deputy State and County Health Officers and with the County Council sitting as the Baltimore County Board of Health, is fulfilling all expectations. Evidence of this is the progress already made in departmental reorganization, environmental health, school health services, public health nursing, mental health services, sanitation, and public relations.

The Association approved a resolution to endorse the specific recommendations outlined in the Stebbins Report, which reads as follows: "That the expanding non-public medical resources becoming available in the county as new general hospitals are constructed be utilized to provide additional out-patient consultation and in-patient psychiatric services. Where possible, this may be done by persuasion and education by the health officer."

Don't throw away your used medical journals. **Charles H. Williams, M.D.,** Pikesville, has sponsored a project whereby these are sent abroad. At the March meeting he read a letter of gratitude from Dr. Macahan of Singapore. Before discarding your medical periodicals, please contact Dr. Williams. Many another Dr. Macahan may be anxious to have them and thus learn more about the advances of American medicine.

CARROLL COUNTY MEDICAL SOCIETY

DANIEL I. WELLIVER, M.D.

Journal Representative

At a recent meeting of the Carroll County Medical Society, the following officers were elected: President, **Howard Hall, M.D.;** Vice president, **James T. Marsh, M.D.;** Secretary-treasurer, **J. H. Caricofe, M.D.;** Journal representative, **Daniel I. Welliver, M.D.**

Plans for the new Carroll County General

Hospital were discussed, and **Mr. McCallum**, the hospital administrator, was introduced. Tentative constitutional bylaws governing the medical staff were presented. **Dr. Dalrymple**, a surgeon and the newly-elected chief of staff, has been working with the bylaws committee and making other plans for the hospital opening, which is set for July 1, 1961.

FREDERICK COUNTY MEDICAL SOCIETY

L. R. SCHOOLMAN, M.D.

Journal Representative

The February meeting of the society was held on the twenty-first at the Francis Scott Key Hotel. **William G. Hardy, Ph.D.**, director of the Hearing and Speech Center of the Johns Hopkins Medical Institutions, spoke on developmental aspects of hearing and language in the infant and preschool child. He gave special attention to currently fruitful screening and test techniques, such as might be applicable in a general preschool health examination. Dr. Hardy showed movies demonstrating techniques in testing the hearing of newborn infants. His wife, who is also his professional associate, joined in the discussion which followed his most interesting presentation.

During the business meeting, the society voted to endorse the educational series of "canned" radio talks which the AMA had sent to WFMD, the local station, but not to have a member of the county medical society preside.

MONTGOMERY COUNTY MEDICAL SOCIETY

CHARLES FARWELL, M.D.

Journal Representative

Luther L. Terry, M.D., a Tulane graduate and a member of our County Medical Society, has been named Surgeon General of the United States. "Enzyme System" research is a current interest of his; his medical papers are considerable. From 1950 to 1958 Dr. Terry was chief of general medicine and experimental therapy at the National Heart Institute; since that time he has been assistant director. Since 1944 he has been an assistant professor of medicine at Johns Hopkins University. Dr. Terry is a member of the American Medical Association, the American Heart Association, and the Medical Advisory Committee of Montgomery County. He is a director of the Montgomery County Tuberculosis and Heart Association and the District of Columbia Tuberculosis Association, president of the District of Columbia Trudeau Society, and is on the editorial staff of the American Heart Journal and the Medical Annals of the District of Columbia. He has been active in the Montgomery County Medical Society. As proud of him as his associates are the members of his family: his wife, the former Beryl Janet Reynolds, and his three children, Janet, Luther, Jr., and Michael.

Edward McGarry, M.D., has been elected president of the Maryland Society of Pathologists.

Brooke A. Beyer, M.D., was certified as a diplomate of the American Board of Otolaryngology.

Our County Medical Speakers Bureau commends the following members for their talks and scientific papers: **Irene Barrett, M.D.**, addressed the freshman class of Randolph Macon College for Women, at Lynchburg, Va., on "Life Planning—Body Mechanic Wise." Dr. Barrett also talked to the P.E.O. group, at the home of Mrs. L. Welch, on "Your Most Valuable Asset." **Thenton D. Boaz, M.D.**, spoke to the Suburban Nurses Club at North Four Corners Recreation Center. His topic: "Contact Lenses, For and Against." **DeWitt E. DeLawter, M.D.'s** "Dietary Treatment of Obese

Diabetics" was presented in the Recent Advances in the Treatment of Diabetes Mellitus program at the Georgetown University Medical Center. **Charles I. Warfield, M.D.,** had published "Abdominal Pregnancy," in the August issue of the Southern Medical Journal; "Uterine Bleeding," in the September issue of Modern Medicine; and "Cytran Therapy, Premenstrual Tension," in the January issue of the Journal of Obstetrics and Gynecology.

The powers who organize meetings for other component medical societies in Maryland may wish to "follow suit" in a training session for medical secretaries, receptionists, technicians, and nurses, such as the one jointly sponsored by the Montgomery County Medical Society, Prince George's County Medical Society, and the Medical and Chirurgical Faculty of Maryland. Knowledge imparted by experts, models, and informal exchanges of experiences was enthusiastically received. In spite of the interrupting snowstorm, more than 100 of these efficient and gracious workers braved the weather hazards to improve their abilities to help sick people and the medical doctor. Popular demand for a "repeat performance" was reported by at least one attendant who was "in the thick of it"—my medical secretary, who served as a model.

"Maynard I. Cohen, M.D., In Memoriam 1915-1961" is quoted from our County Medical Bulletin:

"The Montgomery County Medical Society lost another of its promising young doctors in the death on January 11 of **Maynard I. Cohen.**

"Only 45 years old, Dr. Cohen was Chief of Pediatrics at the Washington Hospital Center. He died of a heart attack while attending a pediatrics meeting in Arlington.

A native of Wilkes Barre, Pennsylvania, Dr. Cohen attended Wyoming Seminary and after graduation from Harvard University went on to Johns Hopkins University Medical School, from which he was graduated in 1940.

"From 1942 to 1946 he was on active duty in the U. S. Navy Medical Corps. Following his discharge with the rank of Lieutenant Commander, he has been engaged in private practice in Silver Spring and on the staffs of several area hospitals, including Suburban Hospital, Children's Hospital and Washington Hospital Center. He was a member of the faculty of George Washington University and a Fellow of the American Academy of Pediatrics.

"Dr. Cohen was most generous with his time and talents on numerous county and regional boards. He was a member of the Board of the Montgomery County Tuberculosis and Heart Association and the Psychiatric Clinic, on the Medical Advisory Committee of the Montgomery County Cerebral Palsy and the National Poliomyelitis Foundation; he was a Pediatric Consultant for Family Service of Montgomery County. He was an active member of the Montgomery County Medical Society, having served on several important committees, and was Treasurer in 1959-1960. He was on the Board of the Washington Hebrew Congregation.

"Continuously studying to keep up with all the newest findings in his and allied fields, he was considered an authority and had contributed articles to leading periodicals.

"Dr. Cohen is survived by his wife, Phyllis; four sons, Lawrence, Alan, Robert and Bruce, of Chevy Chase; his mother, a brother and two sisters. Interment was in the Washington Hebrew Congregation Cemetery."

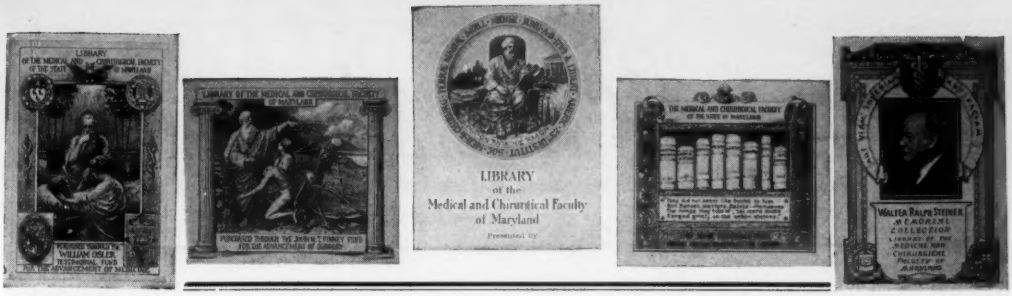
WICOMICO COUNTY MEDICAL SOCIETY

GLADYS ALLEN, M.D.
Journal Representative

The Wicomico County Medical Society held a joint session with the State Trauma Committee of the American College of Surgeons on February 13, 1961. **Henry A Briele, M.D.,** chairman of the Trauma Committee of the Eastern Shore, who had arranged the meeting, introduced **James Jude, M.D.,** of Johns Hopkins Hospital.

Dr. Jude demonstrated the closed chest cardiac massage technique which he and two other doctors had developed in the past three years.

The meeting was open, and nurses, members of the ambulance crew and fire department, and older boy and girl scouts were invited.



Library

Louise D. C. King, *Librarian*

"Books shall be thy companions; bookcases and shelves,
thy pleasure-nooks and gardens." *Ibn Tibbon*

BEAUTY

He hath a daily beauty in his life.
—Shakespeare (Othello Act V Scene I)

DURING THE SNOWSTORMS of the past winter, we drove to and from the Library through some of the most spectacular scenery nature produces in this latitude in which we dwell. Each tiny branch and each blade of grass glistened with its coat of crystal and soft white snow, reflecting myriads of diamonds from the sun, while the arched white trees formed a tunnel of silent loveliness. Yet day in and day out, car after car passed us, the driver's eyes glued to the road and upon his fellow motorists. Not once did we see anyone stop merely to savor the splendor of his surroundings, to stamp on his memory and to steep his soul in the fragile beauty.

May it not be that we, in our hurry to accomplish that which we feel must be done, pay scant attention to events of transcendent beauty during the process? How often do we stop to remember or notice such moments, however fleeting, that must occur during every physician's lifetime? Would not the look in a mother's eyes as her child was cured give strength and courage for the next difficult case and comfort in the event of failure? To see a comatose patient return to normal; to make a clean, life-giving incision; to clear the clouded mind; to view the miracles of birth, with its promise of life, and of death, with its release—these are beautiful and precious experiences. Their remembrance should be a constant stimulus in the daily grind.

Your Library, with its vast resources for increasing knowledge, is always ready to help. As we become more proficient, through constant reading and application of professional literature, these unforgettable moments will be seen more frequently. Let us pause to fortify our souls with these flashes of beauty, lifting our eyes to that transitory loveliness which is so often with us but of which we are not aware.

If eyes were made for seeing,
Then Beauty is its own excuse for being.
The Rhodora
—Ralph Waldo Emerson

The SMITH COLLEGE CLUB
OF BALTIMORE
announces its
THIRD ANNUAL
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BOOK
SALE
at the
NORTH AVENUE MARKET
8 A.M. to 6 P.M.
Thursday, April 20
Friday, April 21
Saturday, April 22
More than 20,000 books of all types at bargain prices. Benefit of the scholarship fund for Baltimore girls.

Maryland
SOCIETY OF PATHOLOGISTS INC.
EDWARD C. MCGARRY, M.D., *President* MANNING W. ALDEN, M.D., *Secretary*
Annapolis, Md.

LONG TERM STORAGE OF FROZEN RED CELLS

THE MOST SIGNIFICANT development in blood preservation since the ACD solutions undoubtedly has been the glycerol method of frozen red cell storage. Unlike the anticoagulant-preservative formulae proposed since ACD, glycerol freezing permits storage of red cells for years, not just for additional days or weeks. Extension of the dating period of blood from the present twenty-one days in ACD solution to a possible five years in glycerol will permit fuller development of blood component therapy and will allow stockpiling of blood for civil and military emergencies.

Glycerol, by permeating the red cells, prevents the damaging effects of ice crystal formation during freezing and thawing. If red cells are maintained at low temperatures in glycerol, transfusion viability is conserved almost indefinitely. Once glycerol has permeated the red cells, however, contact with isotonic solutions will produce hemolysis. Deglycerolization of the blood must proceed by a stepwise exposure of the red cells to decreasing concentrations of glycerol. These steps of deglycerolization might have precluded sterile preparation of red cells for transfusion had not the development of a sterile continuous flow centrifuge suitable for deglycerolization paralleled interest in frozen storage.

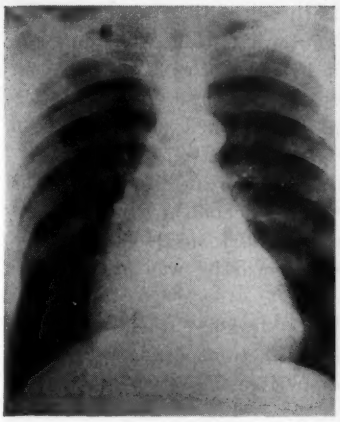
At present, deglycerolization can be safely accomplished by the Cohn Blood Fractionator, which makes use of continuous flow principles. It can accomplish both glycerolization and deglycerolization. Using such equipment, the U. S. Naval Hospital at Chelsea, Massachusetts, has demonstrated that the banking of glycerolized red cells for transfusion is both practical and therapeutically advantageous. Glycerolized red cells have been used for routine operations, for exchange transfusions, and for priming the pump in open-heart surgery. Clinical evidence indicates that serum hepatitis is not transmitted by glycerolized blood. Presumably, the process of deglycerolization completely separates the frozen red cells from plasma, thereby reducing the concentration of hepatitis virus available for transfer.

A need for exceptionally rare types of blood always exists and is difficult to meet without long-term storage. In some instances, only a few donors in the entire country have blood compatible for transfusion to a sensitized patient. By pooling the resources of many blood banks throughout the nation, rare donors can be found; and by stockpiling enough frozen blood, emergency needs can be met. The American Association of Blood Banks, in cooperation with the Chelsea Naval Hospital and the National Institutes of Health, has launched a national program of glycerolized blood storage. These institutions are presently collecting and freezing selected rare types of blood by the glycerol method.

While the glycerol procedure is currently the only feasible method for long term storage of red cells for transfusion, other methods of freezing, still under investigation, may eventually prove more practical. Until the problems of cost, time and complexity of the glycerol method are solved, most blood will continue to be preserved in the ACD solutions.

MARYLAND RADIOLOGICAL SOCIETY
ORGANIZED 1953

Editor—William E. Peterson, M.D.



PA view of the chest



Lateral view of the chest

CASE OF THE MONTH

This is a 48-year-old male who has had substernal discomfort for five years. The PA chest view shows a smooth double density beside the entire right side of the heart. The cardiac border can be seen medial to the right lateral margin of the superimposed density. The lateral view reveals the density to be a fusiform mass lying behind the heart.

What is your diagnosis?
Turn to page 219 for the answer.

Obstetrical Pelvimetry

CEPHALOPELVIMETRY is one of the adjuvants used in determining the possibility of a spontaneous delivery. Other factors involved are uterine force, amount of molding, availability of compensatory space, fetal abnormalities, fetal position, systemic disease, and general health of the mother. The extent to which the referring physician will be influenced by anatomical x-ray measurements will vary with the patient.

Experience has shown that cephalopelvimetry is of value in reassuring that the dimensions of the bony pelvis are sufficient for a spontaneous delivery in a questionable case. It is equally true, however, that errors most frequently occur in the cases where help is most needed; the cases of cephalopelvic disproportion due either to the borderline pelvis or to the unsuspected large baby in the average pelvis. Various methods are used in the roentgen evaluation, all about equal in accuracy; generally, the method used is not as important as the physician using it.

Cephalopelvimetry of the expectant mother at term involves the least hazard to the fetus. Roentgen examinations during the first trimester should be avoided, if possible, since the fetus is most susceptible to irradiation during this period.

Roentgen dosage should be kept at a minimum at all times. This may be accomplished by using minimal exposures, proper filtration, high speed screens and films, and high kilovoltage technique.

In spite of the controversial aspects regarding the use of radiation during pregnancy, cephalopelvimetry at term or in the early stages of labor is a worthwhile and accepted procedure in indicated cases.

James Lyons, M.D.

BALTIMORE CITY HEALTH DEPARTMENT

HUNTINGTON WILLIAMS, M.D.
COMMISSIONER

P. O. Box 1877 Baltimore 3, Md. Plaza 2-2000: Extension 307

Learn To Do Your Part In The Prevention Of Disease

Robert E. Farber, M.D., becomes Assistant Commissioner For Preventive Medicine

On February 9, Robert E. Farber, M.D., was promoted to the position of Assistant Commissioner of Health for Preventive Medicine in the Baltimore City Health Department. He succeeds Mark V. Ziegler, M.D., who retired on January 31.

Dr. Farber was formerly director of the Bureau of Communicable Diseases. In that post he was responsible for the programs for control of smallpox by vaccination, diphtheria and poliomyelitis by inoculation, and control of other diseases such as pertussis, rabies, and tetanus. At the same time he has directed the Health Department control services for tuberculosis and the venereal diseases.

As Assistant Commissioner of Health for Preventive Medicine, Dr. Farber will be in charge of the work, investigations, and community education efforts of nearly all of the City Health Department's chief medical bureaus, including maternity and child hygiene, school hygiene, communicable diseases, dental health, and services for the handicapped. The medical care program is not included.

Dr. Farber is a Baltimorean. He received his education at the Gilman School, at Princeton University, and finally at the Johns Hopkins School of Medicine, from which he was graduated in 1943.

During World War II Dr. Farber was a medical officer on an attack transport in the Pacific. After his separation from the service, he became resident in obstetrics at Bon Secours Hospital, working in the prenatal and postnatal clinics as

arlidin
increases blood flow to the brain in the "senility syndrome" associated with cerebrovascular insufficiency



well as in the general obstetrical service. Before coming to the City Health Department, Dr. Farber was in general medical practice at Sparrows Point for eight years.

Joining the City Health Department staff in July 1955, Dr. Farber became district health officer for the Southern Health District. The following year, having secured the degree of Master of Public Health at the Johns Hopkins School of Hygiene and Public Health, he served as district health officer for the Western Health District. At the end of May 1957, he was appointed director of the Bureau of Communicable Diseases.

Mr. Elkins W. Dahle, Jr., is Director of the Bureau of Industrial Hygiene

On January 12, Mr. Elkins W. Dahle, Jr., was promoted to the position of director of the Bureau of Industrial Hygiene in the City Health Department, filling the vacancy created by the departure of Mr. Charles E. Couchman. Mr. Couchman resigned on October 20, 1960, to join the staff of the U. S. Atomic Energy Commission. For the past five years Mr. Dahle was senior civil engineer in charge of the bureau's Division of Air Pollution Control. He had been acting director of the bureau since August 1960.

Mr. Dahle was born in Baltimore on October 31, 1925, and attended the city public schools. At the Maryland Institute he studied engineering drawing and received a diploma in June, 1945. While at the Maryland Institute he was honored with the Francis Burns Harvey Prize. In 1957 he graduated from Johns Hopkins University with a B. S. degree in civil engineering.

Mr. Dahle has worked with the City of Baltimore since November 1, 1947, having started as principal draftsman with the Department of Planning. He transferred to the Bureau of Sewers as a junior engineer in June 1952. Prior to coming to work for the city, he was employed for three years in private industry as an engineering draftsman.

Mr. Dahle is a member of the American Society of Civil Engineers, the Maryland Society of Professional Engineers, the American Conference of Industrial Hygienists, and the American Industrial Hygiene Association.

Huntington Williams, M.D.
Commissioner of Health



Inadequate cerebral blood flow—often due to cerebral arteriosclerosis—ma result in the "senility syndrome" with its pattern of mental confusion, mem ory lapses, depression, fatigue, apathy and behavior problems.[1-3]

43% increase in cerebral blood flow with Arlidin

In patients with cerebrovascular insufficiency, Eisenberg[4] measured a 43 pe cent increase in blood flow in the brain following administration of Arlidi orally for more than two weeks beginning with a dosage of 12 mg. t.i.d. an increasing to 18 mg. t.i.d. There was a decrease in cerebral vascular resis ance in most instances.

Winsor and associates[3] found Arlidin "of particular value clinically in relie ing some of the symptoms of cerebral vascular insufficiency (vertigo, ligh headedness, mental confusion, diplopia)."

Arlidin is a unique and dynamic vasodilator which acts to increase circulatio in the brain...in the inner ear and eye...also in the peripheral skeletal muscle

arlidin®

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references: 1. Madow, L.: Penn. M. J. 62:861, June 1959. 2. Stieglitz, E. J.: Geriatric Medicin ed. 2, Philadelphia, Saunders, 1949 p. 274. 3. Winsor, T., et al.: Amer. J. Med. Sciences 239:59 May 1960. 4. Eisenberg, S.: ibid, July 1960.

NOTE—before prescribing ARLIDIN the physician should be thoroughly familiar wi general directions for its use, indications, dosage, possible side effects and contrainc cations, etc. Write for complete detailed literature.

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The Heart Page

A SERVICE OF THE HEART ASSOCIATION OF MARYLAND

Luis F. Gonzalez, M.D.—*Editor*

OPEN HEART SURGERY AND THE BLOOD BANK —MUTUAL PROBLEMS

Carroll L. Spurling, M.D.*

TECHNIQUES FOR EXTRACORPOREAL circulation using pump-oxygenators have made open heart surgery a reality. No longer need we be skeptical about its role in treating certain forms of cardiac disease; rather, we can anticipate more extensive procedures as improvements in techniques and equipment make possible circulation bypasses for still longer periods.

As with other advances, satellite problems have arisen, not the least of which are those of concern to the blood bank director. All too often the surgeon is thwarted in his efforts because of a lack of an adequate supply of the fresh compatible blood required. The quantity needed varies from ten to twenty-five pints for each patient. As many as five or six pints are needed to "prime" the pump alone; blood loss from the surgical procedure itself requires rigid replacement; finally, some reserve must be on hand in anticipation of unexpected needs.

The unique features and demands of pump-oxygenators create certain changes in the blood flowing through them; indeed, it seems unlikely that mechanical equipment will ever equal the atraumatic qualities of natural circulation. All of those in current use cause some degree of hemolysis, with plasma hemoglobin values reaching as high as 200 milligrams per cent. Thrombocytopenia occurs regularly, the patient's platelet count frequently falling to one-half of its original level and occasionally lower. Fortunately, clinical bleeding from this alteration alone is rare. A transient leukopenia usually develops but does not appear to have clinical significance. Intravascular clotting may result if anticoagulation is incomplete, and the thromboplastin which is released may consume essential clotting factors. Fibrinolysins may be activated.

Some of these undesirable features have been minimized by special attention to cleanliness of all equipment, by using disposable parts whenever possible, and by making all internal surfaces non-wettable. Because of the large volume of transfused blood required, amounting to a fairly complete exchange transfusion, the quality of the blood has a decided influence on the magnitude of the changes. Red blood cells become more susceptible to osmotic and mechanical lysis upon storage under blood bank conditions. The platelet count falls quickly, and it is known that large volumes of bank blood transfused for any reason can greatly lower the platelet count of the recipient. Certain coagulation factors, such as antihemophilic globulin and proaccelerin, diminish relatively rapidly. The only available means to partially circumvent these storage effects is the use of blood which is as fresh as possible. Heparin is used as an anticoagulant because it avoids dilution of the blood, allows near normal ionized calcium and electrolyte composition, and can be

(*Continued on page* 219)

*Associate professor of medicine, University of Maryland School of Medicine.

MARYLAND TUBERCULOSIS ASSOCIATION

Christmas Seal Agency for State of Maryland

900 ST. PAUL STREET • BALTIMORE 2, MARYLAND

TUBERCULOSIS FACTS AND FIGURES

ALTHOUGH THE MARYLAND Tuberculosis Association is primarily concerned with the control of tuberculosis within the state, it must stay alert to the problems which confront all parts of the country. The Research and Statistics Division of the National Tuberculosis Association has compiled information which indicates the scope of the tuberculosis situation. Twenty-five hundred affiliated voluntary tuberculosis associations are conducting programs, made possible by the traditional Christmas Seal Campaign, directed toward eventual solution of the problem.

The facts uncovered by the NTA investigations are further proof that here in the middle of the twentieth century, the disease persists as in the past.

In 1958 the rate of new active cases and deaths among men was double that for women. The rate among colored races was about three times as high as among Caucasians; on the other hand, about half of all new active cases and deaths occurred among white men. In that same year, eighteen large American cities with only one-sixth of the population of the continental United States had more than one-fourth of the newly reported active cases and tuberculosis deaths. Some 2,500 Americans who died of tuberculosis that year had not been previously reported as having active disease. Since 1958, Baltimore has moved to its unenviable position at the top of the list of large cities in tuberculosis incidence.

The following three tables illustrate the prevalence of tuberculosis and case and death rates for the continental United States in recent years.

1. The estimated prevalence of tuberculosis cases in 1956 was as follows:

	Total	Known	Unknown
Total cases	800,000	400,000	400,000
Active	250,000	150,000	100,000
Inactive	550,000	250,000	300,000

In addition, there were an estimated 1,200,000 persons who once had tuberculosis.

2. From 1958 to 1959, the new active case rate declined 12 per cent, and the death rate declined 6 per cent.

Year	Newly reported active tuberculosis cases		Deaths from tuberculosis	
	Number	Rate per 100,000	Number	Rate per 100,000
1959 (provisional)	56,709	32.2	11,730	6.7
1958	63,000	36.4	12,361	7.1
1957	66.437	39.0	13,324	7.8
1956	68.866	41.2	14,061	8.4
1955	76,245	46.4	14,940	9.1

3. The tuberculosis case rates and death rates in 1958 were as follows:

Rate per 100,000	Age in years					
	Under 5	5-14	15-24	25-44	45-64	65 and over
New active case rate	12.6	6.8	26.6	43.4	59.2	73.3
Death rate	1.0	0.2	0.9	4.8	14.3	30.6

The following tables relate to areas beyond our continental limits: Alaska, Hawaii, and Puerto Rico.

1. Newly reported active tuberculosis cases and case rates per 100,000 population:

Year	Alaska		Hawaii		Puerto Rico	
	Number	Rate	Number	Rate	Number	Rate
1958	256	134.0	278	44.0	2,313	99.7
1957	431	204.3	281	45.8	2,551	111.8
1956	595	288.8	434	74.3	2,924	129.0
1955	661	322.4	462	85.4	3,396	149.5

2. Tuberculosis deaths and death rates per 100,000 population:

	Alaska		Hawaii		Puerto Rico	
	Number	Rate	Number	Rate	Number	Rate
1958	19	9.9	37	5.9	667	28.7
1957	46	21.8	20	3.3	741	32.5
1956	41	19.9	35	6.0	825	36.4
1955	41	19.6	35	6.3	746	33.0

3. Newly reported active tuberculosis cases and case rates per 100,000 population, by age, in 1958:

Age groups	Alaska		Hawaii		Puerto Rico	
	Number	Rate	Number	Rate	Number	Rate
All ages	256	134.0	278	44.0	2,313	99.7
Under 5 years	15	41.7	1	1.3	261	76.1
5-14 years	39	114.7	5	3.8	230	38.2
15-24 "	51	136.8	21	18.9	345	82.8
25-44 "	82	159.6	104	56.1	698	145.3
45-64 "	38	158.3	102	108.4	506	149.9
65 years and over	29	414.3	42	148.3	236	228.6
Age not stated	2		3		37	

4. Newly reported active tuberculosis cases and case rates per 100,000 population, by race and sex, in 1958[1]:

Race and sex	Alaska		Hawaii	
	Number	Rate	Number	Rate
Total	256	134.0	278[2]	44.0
White	40	26.3	22	15.2
Male	28	28.3	12	14.5
Female	12	22.6	10	16.1
Nonwhite	216	553.8	255	52.6
Male	131	623.8	173	65.9
Female	85	472.2	82	36.8

[1] Race and sex data not available for Puerto Rico.
[2] Includes one not reported as to race and sex.

The continuing impact of tuberculosis against American citizens has been made clear. The need for continuing control programs by the tuberculosis associations has been similarly demonstrated.

Open Heart Surgery and the Blood Bank

(*Continued from page* 216)

neutralized readily with protamine. It is not satisfactory, however, if the blood is to be stored. For these reasons most surgeons prefer to have blood drawn from donors on the same day as surgery.

Although efforts to refine techniques and to improve equipment are continuing, the logistic problems of blood procurement are major ones and will undoubtedly remain with us. Not only are patients' relatives asked to find fifteen or twenty donors, but the donors must be of the same blood group as the patient. They must be willing to come to the blood bank before the day of surgery to give a blood sample for typing and crossmatching and to return early on the morning of surgery to donate the blood. If the patient is fortunate enough to be of blood group O or A Rh positive, a pool of 40 or 45 random potential donors would supply, statistically speaking, 15 donors of the right type. If the patient happens to be AB Rh negative, a pool of 2,000 random donors would be required! Few of us could cope with such odds. It has become obvious that the entire program of open heart surgery depends on widespread public support and that the aid of large organized donor groups must be enlisted.

JET CHARTER TO EUROPE

July 19-August 14

Again this year the Medical and Chirurgical Faculty is chartering a flight to Europe, via Air France 707 jet, at the incredibly low rates of $300.00 per person for tourist class and $340.00 first class. (All service is first class, the difference being in location of seats.) The flight will leave Friendship Airport on the evening of July 19, landing in London the following morning. The return flight will depart from Paris on August 14 and land at Idlewild Airport, New York, that afternoon.

A joint clinical conference with the British Medical Society is again being planned, after which you may travel independently or join the deluxe escorted tour being prepared by Towson Travel Center in cooperation with American Express.

Reservations are limited and must be in before May 1. Only Faculty members and their immediate family are eligible. A reservation form will be found in the Executive Secretary's Newsletter (Page A17-18). Return it now with a $100.00 deposit for each person.

Case of the Month X-Ray Diagnosis:

Achalasia of the esophagus. The esophagus is filled with non-opaque substance. Confirmed by barium swallow.

Woman's Auxiliary
Medical and Chirurgical Faculty

MRS. E. RODERICK SHIPLEY *Auxiliary Editor*

APRIL, 1961

NOW'S THE TIME! Plan to attend
THE 1961 ANNUAL CONVENTION

of the Woman's Auxiliary to the Medical and Chirurgical Faculty of Maryland

WHEN? April 26 and 27

WHERE? Sheraton Belvedere Hotel

WHY? Because . . .

Your convention chairman has arranged a most interesting program for you. Registration will begin at 9:30 A.M. Wednesday the 26th. Early arrivals will find hot coffee awaiting them.

A general meeting will be called to order at 10:00, at which time county auxiliary presidents and chairmen of standing committees will give their annual reports. Mrs. William Mackersie, president of the Women's Auxiliary to the AMA, will install the new officers; and Mrs. Norman Oliver, of Silver Spring, will assume the presidency of our state auxiliary. The presidents and presidents-elect of the auxiliaries of New Jersey, Delaware, Pennsylvania, West Virginia, Virginia, the District of Columbia, and the Southern Medical Association have been invited as guests.

A social hour will precede the 12:30 luncheon in the Charles Room. Fashions from the Dorothy Lovell Shop will be modeled by Auxiliary members. Climaxing the afternoon will be a trip to Sherwood Gardens, for which transportation has been arranged.

Thursday's activities will begin with the past presidents breakfast, after which Mrs. Oliver will conduct her first board meeting. A two-hour shipboard tour of Baltimore Harbor will begin at 1:30 in the afternoon. The *Port Welcome* holds 600 people, and the physicians are invited to come along.



A WELCOME GUEST at our annual meeting will be Mrs. William Mackersie, of Detroit, Michigan, president of the Woman's Auxiliary to the American Medical Association. We'd like you to meet her.

She worked as a county auxiliary member for 27 years and in 1951-52 was president of the Michigan state auxiliary. In 1958-59 she was north central

The annual banquet of the Medical and Chirurgical Faculty takes place Thursday evening, and we will join the men for this event.

1961 CONVENTION COMMITTEE

Chairman
Mrs. Charles H. Williams

Hospitality
Mrs. Ross Pierpont

Flowers
Mrs. Conrad Acton

Fashion Show
Mrs. Raymond V. Rangle

Tickets and Registration
Mrs. D. D. Caples

Hotel
Mrs. Roger Windsor

Transportation
Mrs. Walter Hammett

regional vice president of the national auxiliary. Her chairmanships in the national auxiliary include resolutions for the 1952 conference and the 1953 convention, civil defense in 1953-55, and revisions in 1958. She was a director in 1955-57.

A native of Canada, Mrs. Mackersie met her husband, an anesthesiologist, during World War I. She was working in Ottawa, where he was stationed. Dr. and Mrs. Mackersie have a son and a daughter, both married, and three grandchildren.

Mrs. Mackersie is a registered parliamentarian and has served in this capacity for the Michigan Parent-Teacher Association, the Detroit P.T.A. Council, and the Michigan Division of the National Farm and Garden. She is a member of the National Association of Parliamentarians.

Her leisure time interests are figure skating, early American dancing, and knitting.

No Auxiliary in Your County? Be a Member-at-Large

ARE YOU A DOCTOR'S wife who would like to meet and become better acquainted with other doctors' wives? Would you like to learn more about your role in the community as a doctor's wife? If you have your role well established, would you be willing to share your valuable experience with the newer wives? Have you any interest in health education, medical careers, research, civil defense, public welfare, self-enlightenment? If your answer to any of these questions is *yes,* then you should become a member of the Woman's Auxiliary of your county medical society or of the Medical and Chirurgical Faculty of Maryland.

It's easy to become a member. Simply write, stating your case, to Mrs. Emil G. Bauersfeld, 3916 Virgilia Street, Chevy Chase 15, Maryland.

As chairman of the members-at-large, I have this year sent letters of invitation to many physicians' wives who are not members. Several have accepted the invitation to join. I should like to extend this invitation to the remaining doctors' wives in Maryland to become a member of the Woman's Auxiliary.

On January 11, 1961, the Talbot County Medical Society gave its approval to the formation of a Woman's Auxiliary in that county. This will remove a number of names from the members-at-large roll, but it will bring more doctors' wives into active Auxiliary. We would like to see this happen in the other counties of the state which do not already have a fully organized Auxiliary. Until such an ideal situation exists, however, we shall continue to make it possible for every doctor's wife to help her husband and her community by joining the Woman's Auxiliary to the Medical and Chirurgical Faculty of Maryland as a member-at-large.

At the present time, the Maryland Auxiliary membership includes approximately 120 members-at-large in addition to those members of the five organized or about to be organized county units.

"To preserve and enhance the heritage of American medicine is a privilege designed especially for our organization" is the current

slogan of the Woman's Auxiliary to the American Medical Association. Maryland's own slogan, "Handmaidens to Health," also suggests the role you may play as an Auxiliary member. Through the Auxiliary, a doctor's wife may come into closer contact with her husband's interests and work and gain a greater understanding of the problems faced by our doctors. Experiences peculiar to doctors' wives may be shared, and answers to problems that arise from time to time may be found. Won't you at least explore the subject further by asking whatever questions you might have about the Auxiliary? We are certain that you would enjoy being one of us just as much as we would enjoy having you.

Arlene E. Baybutt



Introducing

Our County Presidents

Mrs. Edward C. Loo, President
Woman's Auxiliary to the
Harford County Medical Society

SHIRLEY M. LOO, first president of the Woman's Auxiliary to the Harford County Medical Society, was born in Easton, Pennsylvania. She was employed as record librarian in Easton Hospital when she met Edward C. Loo, M.D., a resident under the training program of the New York University-Bellevue Medical Center. They were married in January 1952 and now reside in Havre de Grace, Maryland. They have two daughters.

Shirley was among those who helped to organize the Woman's Auxiliary to the Harford County Medical Society. She has been interested in hospital auxiliaries for many years and, while still in Pennsylvania, she was an active member of the Junior Woman's Auxiliary of the Easton Hospital.

This spring Harford County celebrates its first anniversary as a member Auxiliary.